D_2 Receptor Imaging with Iodine-123-Iodobenzamide Brain SPECT in Infants with Hypoxic-Ischemic Brain Injury

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The purpose of this study was to evaluate the striatal dopamine D_2 receptor density in infants with perinatal hypoxic-ischemic brain injury (HIBI) using ^{123}I-iodobenzamide (IBZM) brain SPECT and to correlate the findings with the severity of HIBI and neurologic outcome. **Methods:** Twenty infants who were diagnosed to have perinatal HIBI were included in this study. They were classified as having mild (n = 6), moderate (n = 10) or severe (n = 4) HIBI according to their neurologic findings at birth using the criteria of Sarnat and Sarnat. Neurologic outcome of these infants was determined by serial neurologic examinations and the Denver developmental screening test; 10 infants recovered without any deficit and the remaining 10 were affected to a degree varying from motor impairment to cerebral palsy. All 20 infants were examined using ^{123}I-IBZM brain SPECT at age 7.8 ± 2.3 mo. Transaxial slices were obtained 2 hr after intravenous injection of 300 μci (11.1 MBq) ^{123}I-IBZM and the activity ratios of striatal to occipital cortex (ST/OC) were calculated. **Results:** The mean ST/OC ratios in patients with mild, moderate and severe HIBI (1.219 ± 0.078, 1.097 ± 0.069 and 0.813 ± 0.140, respectively) were significantly different from each other (p = 0.001). The infants who recovered from HIBI without any neurologic sequelae had higher mean ST/OC ratios than the others (1.184 ± 0.010 versus 0.969 ± 0.160, p = 0.002). **Conclusion:** The results of this study show that in infants with HIBI, striatal D_2 receptor density decreases as the severity of injury increases. The D_2 receptor density is higher in infants who recover without neurologic deficits compared to those who are affected neurologically. Dopamine D_2 receptor imaging can be used to assess the severity of HIBI in children.

Key Words: hypoxic-ischemic brain injury; perinatal asphyxia; iodine-123-iodobenzamide; SPECT

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The static encephalopathies of childhood are common disorders, affecting approximately 1 per 500 children (*1*). Hypoxic-ischemic brain injury (HIBI) is one of the few identifiable and potentially treatable causes. In addition to a variety of neurodevelopmental impairments, individuals who survive neonatal HIBI often exhibit abnormalities of the basal ganglia (*2–5*). The corpus striatum is particularly vulnerable to hypoxic injury (*6,7*).

The cerebral injury observed in humans has been modeled in rats by inducing HIBI after unilateral ligation of the carotid artery and hypoxia (*8,9*). Using the rat HIBI model and autoradiographic techniques, several investigators have shown that neonatal HIBI causes a decrease in striatal dopamine D_1 and D_2 receptor densities (*10,11*). It also has been shown that the density of striatal D_1 receptors returns to normal 9–11 wk after the injury; however, the loss in D_2 receptors is permanent (*12,13*). More recently Zouakia et al. (*14*) studied ^{125}I-labeled iodobenzamide (IBZM) dopamine D_2-receptor binding in rats with no visible loss of hemispheric volume for in vitro and ex vivo autoradiographic experiments. They showed a 40% decrease in the striatal binding of D_2 receptors after HIBI, in contrast to no modifications of D_1. In another study, D_2 receptor status was evaluated with ^{123}I-IBZM SPECT in patients with a history of cerebral hypoxia caused by cardiac arrest or coronary artery bypass surgery under cardiopulmonary bypass. The results suggested that striatal D_2 receptor status may be a sensitive indicator of cerebral hypoxia (*15*).

The purpose of this study was to evaluate the striatal dopamine D_2 receptor density in infants with perinatal HIBI using ^{123}I-IBZM brain SPECT and to correlate the findings with the severity of HIBI and neurologic outcome.

MATERIALS AND METHODS

Patients

Twenty infants with HIBI were examined using ^{123}I-IBZM brain SPECT at age 7.8 ± 2.3 mo (Table 1). All infants had a history of perinatal asphyxia that was defined as meeting at least two of the following criteria: (a) documentation of intrapartum fetal distress on fetal heart-rate monitoring, with or without the presence of meconium staining of the amniotic fluid; (b) the presence of an Apgar score below 6 at 5 min, and/or cord blood pH taken shortly after the delivery below 7.20; and (c) need for more than 1 min of positive pressure ventilation before sustained respiration occurred. All infants had clinical signs of postpartum encephalopathy such as seizures, hypo- or hypertonia, pathological spontaneous movements, lethargy or coma during the first 48 hr of life.

Preterm infants and infants with congenital anomalies of the central nervous system, chromosomal abnormalities or transitory drug depression, sepsis and hypoglycemia were excluded from the study.

Clinical Assessment

Patients were staged as mildly, moderately or severely affected depending on the clinical findings at birth according to the criteria of Sarnat and Sarnat (*16*). Generally, neonatal encephalopathy associated with perinatal asphyxia has been described in three stages: Stage 1 (mild): hyperalertness, hyperexcitability; Stage 2 (moderate): lethargic or obtunded level of consciousness, hypotonia, suppressed primitive reflexes; and Stage 3 (severe): stupor or coma, flaccidity, absent primitive reflexes.

Neurological outcome of these infants was determined as: 1, normal outcome; 2, motor impairment (abnormality in muscular

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TABLE 1
Clinical Characteristics and CT and Iodobenzamide SPECT Findings

Patient no.	Sex	Age at SPECT (mo)	Clinical features	Sarnat stage	CT findings	Mean ST/OC	Antiepileptic	Neurologic outcome
1	M	10	Hypotonia, weak reflexes	1	Normal	1.291	–	Normal
2	F	9	Hyperexcitability	1	Normal	1.271	–	Normal
3	M	10	Hyperexcitability	1	Normal	1.266	–	Normal
4	F	6	Hyperexcitability	1	Normal	1.237	–	Normal
5	F	10	Hypotonia, lethargy	2	Normal	1.228	–	Normal
6	F	4	Hyperexcitability	1	Normal	1.152	–	Normal
7	F	4	Hypotonia	2	Normal	1.141	+	Motor impairment
8	F	4	Hypotonia, weak reflexes	2	Normal	1.127	+	Normal
9	F	10	Hypotonia, lethargy	2	Parasagittal hypodensity	1.126	+	Motor impairment
10	F	4	Hypotonia, lethargy	2	Normal	1.117	+	Motor impairment
11	M	9	Hypotonia	2	Normal	1.112	–	Normal
12	F	10	Hyperexcitability	1	Normal	1.095	–	Normal
13	M	10	Hypotonia, weak reflexes	2	Normal	1.059	–	Normal
14	M	5.5	Hypotonia, lethargy	2	Normal	1.055	+	Motor impairment
15	M	8	Hypotonia, absent reflexes	2	Normal	1.021	+	Motor impairment
16	M	9	Hypotonia, lethargy	2	Normal	0.983	+	Motor impairment
17	M	10	Flaccidity, lethargy	3	Parasagittal hypodensity	0.969	–	Motor impairment
18	M	8	Flaccidity, absent reflexes	3	Widespread hypodensity	0.896	+	Spastic CP, MMR
19	F	8	Flaccidity, absent reflexes	3	MCE	0.702	+	Spastic CP, MMR
20	M	9	Flaccidity, stupor	3	PVL	0.683	–	Spastic CP, MMR

ST = striatum; OC = occipital cortex; CP = cerebral palsy; MMR = mental motor retardation; MCE = multicystic encephalomalacia; PVL = periventricular leukomalacia.

tone or pattern of motor development); or 3, cerebral palsy (diplegia, hemiplegia or tetraplegia) by means of serial neurologic examinations and the Denver developmental screening test (Table 1) (*17*).

Informed consent was obtained from the parents, and the study was approved by the institutional board and the authorities.

Iodine-123-Iodobenzamide SPECT

Based on the medical internal radiation dose method (MIRD) applied to the combined data of six volunteers by Verhoeff et al. (*18,19*) and five volunteers by Kung et al. (*20*), radiation dose estimates for ^{123}I-IBZM (mSv/MBq) were established for healthy volunteers aged between 5 yr and adult. For adults, it seems that none of the organs would present a particular problem because the thyroid absorbs ~5 times more radiation in 5-yr-old children than in adults (0.86 mSv/MBq versus 0.16 mSv/MBq). Therefore, an intensive thyroid-blocking scheme was performed. Potassium iodine (KI) in a 10% solution was given to children to inhibit thyroid uptake of ^{123}I (3 × 15 droplets during the 2 days preceding the scan, 20–30 droplets on the morning of the day of the scan and advised to continue KI for at least 3 days after the scan).

Chloral hydrate (25–50 mg/kg) was administered orally for sedation (*21*). Nine of the 20 patients were taking antiepileptic medication (5 mg/kg phenobarbital) during the SPECT study, but none of them was taking any D_2 receptor-blocking agents that could have interfered with the study (Table 1).

A total activity of 300–400 μCi ^{123}I-IBZM was administered intravenously, and brain SPECT was performed 2 hr after intravenous injection with a dual-head rotating gamma camera (Optima Nx 5800409DG; GE Medical Systems, Milwaukee, WI) equipped with super-high-sensitivity collimator resolution; 17.3 mm at 100 mm sensitivity: 1085 cts/min/μCi at 100 mm). Images of the head were acquired over 64 angles through 360° angle with each image being collected for 20 sec with a zoom factor of 1.33. Total acquisition time was approximately 20 min. Data were stored in a 128 × 128 matrix. Head positioning was done with the help of a projected light source.

Quantification of D_2 Receptor Activity

After image backprojection, image reconstruction was performed using Butterworth and ramp filters with a cutoff frequency of 0.39 and a power factor of 10. Transaxial slices were obtained parallel to the orbitomeatal line. After reconstruction of the transaxial slices, three consecutive slices showing the highest basal ganglia activity were selected. These selected slices were analyzed separately and striatum-to-occipital cortex (ST/OC) ratios were determined from predefined fixed regions of interest (ROIs).

These ROIs (rectangular, 5 × 8 pixel; 1 pixel = 3 mm) were optimally fitted over the ST or its expected location. A control ROI (32 pixel^2) was placed on the occipital cortex in the same slices. The ratio of the mean striatum count density [(left + right)/2] divided by the occipital count density (ST/OC ratio) was calculated for the estimation of dopamine D_2-receptor binding for each slice. The ST/OC ratios obtained for each slice were summed and divided by three to obtain a mean value of ST/OC ratio in each patient. The mean ST/OC ratio data were expressed as mean ± s.d. It has been shown that ST/OC ratios based on fixed ROIs provide the best quantitative estimation of the dopamine D_2-receptor binding potential of the striatum (*22*).

In those patients who had markedly reduced tracer uptake in the striatum, visual evaluation of the brain configuration, distance from the orbitomeatal line and CT scans were used for selecting the slices and placing the ROIs.

Statistical Analysis

The comparisons among three groups were performed using the Kruskal-Wallis test, and comparisons between two groups were performed using the Mann-Whitney U test. Sensitivity and speci-

TABLE 2
Iodobenzamide Binding in Relation to Severity of Injury and Neurologic Outcome

Injury (Sarnat stage)	No. of patients	Neurologic outcome: Without sequelae	Neurologic outcome: With sequelae	IBZM binding mean ST/OC ratio: Without sequelae	IBZM binding mean ST/OC ratio: With sequelae
Mild (1)	6	6	0	1.219 ± 0.078	—
Moderate (2)	10	4	6	1.132 ± 0.070	1.074 ± 0.060
Severe (3)	4	0	4	—	0.813 ± 0.140
Total	20	10	10	1.184 ± 0.080	0.969 ± 0.100

ST = striatum; OC = occipital cortex.

ficity of ^{123}I-IBZM to predict the outcome of children with HIBI were calculated for each measurement of ST/OC ratio on a continuous scale. Receiver operator characteristic (ROC) curve for the test was assessed using the area under the ROC curve as an index of performance. The results were analyzed by the SSPS package according to the ROC methodology of Metz (*23*).

RESULTS

The mean ST/OC ratios in patients with mild, moderate and severe HIBI (1.219 ± 0.078, 1.097 ± 0.069, 0.813 ± 0.140, respectively) were significantly different from each other (p = 0.0014).

The mean ST/OC activity ratio decreased as the degree of HIBI increased (Table 2). Severely affected patients showed almost no specific radioreceptor activity in the striatum (Fig. 1).

Results also were evaluated on the basis of neurologic outcome (Tables 1 and 2). All six infants with mild HIBI were developing normally, free of demonstrable sequelae. Three of the 4 patients with severe HIBI had cerebral palsy and 1 had motor impairment. Neurologic outcome varied in the moderately injured group with 4 patients free of sequelae and the remaining 6 having motor impairment. Overall, 10 children recovered without any deficit and the remaining 10 had some form of neurologic sequelae. The children who had no sequelae had higher mean ST/OC ratios compared with those who had sequelae (1.184 ± 0.084 versus 0.969 ± 0.160, p = 0.002) (Table 2).

The mean ST/OC ratio in infants with normal outcome (n = 10), motor impairment (n = 7) and cerebral palsy (n = 3) were significantly different from each other (1.184 ± 0.084, 1.059 ± 0.071, 0.76 ± 0.100, respectively, p = 0.003).

The sensitivities and specificities of ^{123}I-IBZM for each measurement of ST/OC ratio are shown in Table 3. The performance of the ^{123}I-IBZM SPECT to predict outcome and to distinguish infants who will have neurologic sequelae from infants who will have normal outcome was evaluated by ROC-curve analysis (Fig. 2). The ROC curve for ^{123}I-IBZM brain SPECT showed a large area under the curve that was 0.90 ± s.e. of 0.056.

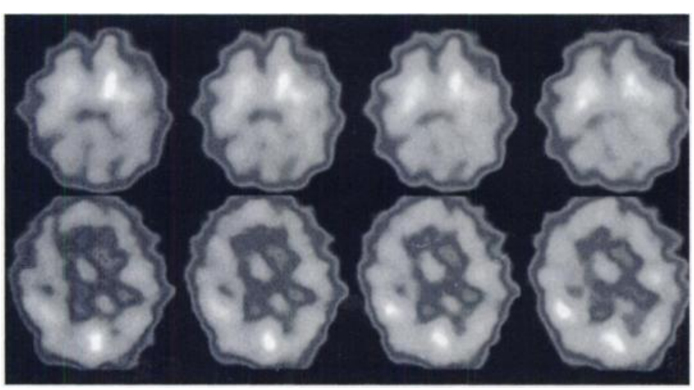

FIGURE 1. Top row: visualization of dopamine D_2 receptor activity in striatum by ^{123}I-IBZM in Patient 3 with mild hypoxic-ischemic brain injury (HIBI). Uptake is almost absent in surrounding cortical brain tissue in sequential transaxial slices. Bottom row: almost no specific uptake is seen in the striatum in Patient 18, who has history of severe HIBI. Uptake in surrounding brain tissue is due to aspecific binding but seems to be increased due to relative scaling of the image.

TABLE 3
Sensitivity and Specificity of Iodine-123-Iodobenzamide Study Compared with Each ST/OC Ratio

Specificity	Sensitivity	ST/OC Ratio
1	0	0
1	0.1	0.683
1	0.2	0.702
1	0.3	0.896
1	0.4	0.969
1	0.5	0.983
1	0.6	1.021
1	0.7	1.055
0.9	0.7	1.059
0.8	0.7	1.095
0.7	0.7	1.112
0.7	0.8	1.117
0.7	0.9	1.126
0.6	0.9	1.127
0.6	1	1.141
0.5	1	1.152
0.4	1	1.228
0.3	1	1.237
0.2	1	1.266
0.1	1	1.270
0	1	1.291

ST = striatum; OC = occipital cortex.

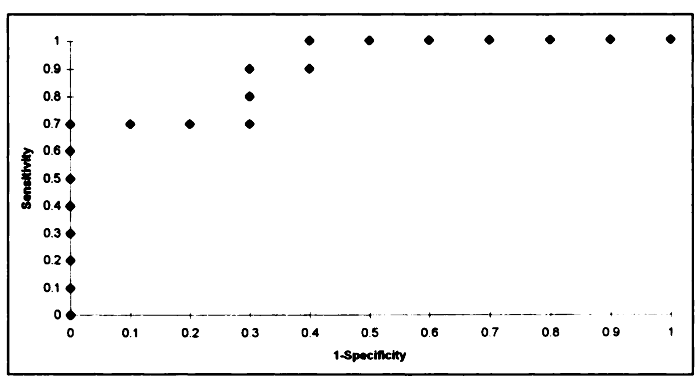

FIGURE 2. Receiver operating characteristic curve (ROC) analysis of ^{123}I-IBZM study. Area under the ROC curve is 0.90 (confidence interval 0.69–1.00).

DISCUSSION

The clinical diagnosis of HIBI in neonates can be supported by radiologic studies including cranial sonography, CT (*24*), SPECT (*25*), MRI (*26*) and PET (*27*). However, none of these modalities is specific for the diagnosis of perinatal asphyxia.

The primary finding in this study was the decreasing ST/OC ^{123}I-IBZM activity ratio in response to increasing degree of HIBI and unfavorable neurologic outcome. Because IBZM specifically binds to dopamine D_2 receptors, this finding indicates a loss or disfunction of D_2 receptors in the striatum of children with HIBI. The comparison leading to this interpretation was made in children with HIBI, and normal values for unaffected children were not available. For obvious reasons, also unavailable were histologic examinations of striatum of the study population. Because histologic examination and comparisons with normal controls were made in the rat model, interpretation of our findings required a review of previous animal studies.

D_2 receptors in striatum may be located on both corticostriatal nerve terminals and on neurons intrinsic to the striatum (*28, 29*) In our study population, HIBI affected not only the striatum but also the cortex. Thus, it is possible that the observed decrease in striatal D_2 receptors is due to either striatal or cortical neuronal cell loss or both. In the rat HIBI model, however, Johnston (*7*) demonstrated that striatal hypoxic ischemic injury was more severe than damage to the overlying cortex. Burke and Karanas (*30*) showed that in moderately affected rats, the striatum was reduced in size, which appeared to be primarily due to the loss of medium-sized striatal neurons.

Because abnormalities predominate at the level of the striatum, Kostic et al. (*12*) and Prezedborski et al. (*10*) suggested that the decrease they observed in the density of striatal D_2 receptors in rats with HIBI was mainly due to intrinsic striatal neuron involvement. The observed decrease in ipsilateral striatal D_2 receptors was significant only in those rat brains that showed an 85% or more shrinkage in volume. In contrast to Kostic et al. (*12*) and Przedborski et al. (*10*), Zouakia et al. (*14*) were able to demonstrate a 40% decrease in the striatal binding of ^{123}I-IBZM on both the ipsilateral and the contralateral sides to carotid ligation in rats that had no discernible difference in the size of the two cerebral hemispheres. They did not, however, provide a satisfactory explanation concerning the bilateral effect of carotid ligation on striatal D_2 receptors.

In our study, all severely affected children, according to Sarnat and Sarnat's staging, had anatomic abnormalities detected by CT, suggesting significant loss of neural tissue. In contrast, only 1 moderately affected and none of the mildly affected patients had abnormalities seen on CT. Although the severely affected patients had the lowest striatal IBZM activity, patients in the moderately affected group also had a significantly reduced activity ratio compared with the mildly affected patients.

We believe that the cause of the decrease in the density of striatal D_2 receptors was most probably the loss of striatal neurons in children with HIBI. However, loss of striatal neurons suggests that this decrease may be present even in the absence of gross morphologic abnormality.

The ability of ^{123}I-IBZM SPECT to detect the decrease in D_2 receptors or the neurons that carry those receptors may make it more useful than other imaging modalities when there is no gross morphologic change in cerebral structures, such as in our moderately affected patients.

Determining the prognosis in neonates with HIBI early in the disease process is important for the management of the patient and for possible future treatment. Mildly affected patients, according to Sarnat and Sarnat (*31*), almost always recover without sequelae, and patients with severe injury have a high rate of permanent dysfunction. However, in patients with moderate injury, the prognosis is unpredictable. D_2-receptor imaging with ^{123}I-IBZM brain SPECT may be particularly suited for such children.

For ethical reasons, normal values for D_2-receptor imaging could not be obtained in healthy infants and is not available elsewhere. The ST/OC ratio of children with HIBI is significantly less than that of normal adults (*23*) reported in the literature, even for mildly affected children who eventually recover completely.

Although the results of this study strongly suggest that ^{123}I-IBZM brain SPECT can be valuable in predicting the prognosis in children with HIBI, its potential use needs to be verified by other studies performed during the neonatal period.

CONCLUSION

As evaluated by ^{123}I-IBZM brain SPECT imaging, increasing degrees of HIBI were related to decreases in striatal dopamine D_2 receptor density in children with perinatal asphyxia. Patients with remaining neurologic impairment had decreased striatal D_2 receptor density compared with those who recovered completely. The results of this study indicate a potential use for ^{123}I-IBZM brain SPECT in determining the prognosis in children with HIBI.

STATISTICAL APPENDIX: THE ROC

The ROC, a technique developed in the field of signal detection, is a graph of the true-positive rate (sensitivity) against the false-positive rate (1 − specificity) for each possible cutoff point or decision threshold. A test result with no diagnostic utility has a diagonal ROC curve; a perfect test result has a curve close to the upper left corner of the graph. The area under the curve is a suitable single quantitative summary of the diagnostic accuracy of the prediction rule. An area near one indicates a test with good sensitivity over a wide range of specificities, thus representing high accuracy. This form of analysis is independent of relative frequencies of events and minimizes the potential bias introduced by choosing a single cutoff for positivity. Hence, ROC curves are being used to judge the discrimination ability of various diagnostic systems for predictive purposes.

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Technetium-99m-HMPAO SPECT and MRI of Brain in Patients with Neuro-Behçet's Syndrome

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Involvement of the brain is one of the most important complications of Behçet's disease (BS). It is difficult to diagnose, however, because of the lack of effective imaging methods. **Methods:** Thirteen BS patients with neuropsychiatric symptoms or signs [Neuro-Behçet's syndrome (NBS)] were included in this study. We combined two routine brain imaging modalities—brain SPECT with ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) and brain MRI—with clinical manifestations to diagnose brain involvement. **Results:** Technetium-99m-HMPAO brain SPECT findings were abnormal in 100% (13/13) of patients. Brain MRI findings were abnormal in 31% (4/13) of patients. Gray matter was involved more commonly than white matter. In the gray matter, the cerebral cortex was the most commonly involved area and the cerebellum was the least commonly involved area in NBS. **Conclusion:** SPECT is a more sensitive and useful tool in detecting brain involvement in NBS patients compared with brain MRI. The combination of HMPAO and MRI is necessary to detect brain lesions in both gray and white matter in NBS.

Key Words: MRI; SPECT; Behçet's syndrome

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Behçet's syndrome (BS) is a rare disorder of unknown etiology and is characterized by recurrent oral and genital aphthous ulcers, ocular inflammation and neurological involvement (*1*). Neurological complications occur in approximately 10%–25% of all patients (*2*). Common neurological manifestations include cerebral venous thrombosis and cerebrovascular accident (*3*). The diagnosis and management of BS with neuropsychiatric symptoms or signs [neuro-Behçet's syndrome (NBS)] are critical (*4,5*). Due to the lack of effective imaging techniques, however, diagnosis of brain involvement in NBS patients is difficult.

MRI has been used to detect structural lesions in NBS patients (*6–8*). The most typical MRI findings in NBS are brain lesions of high signal intensity on T2-weighted images (*6–8*). In a significant proportion of patients with clinically evident brain involvement, however, brain MR images are normal (*9*). SPECT brain imaging with ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) is an alternative modality that is used to assess regional cerebral blood flow (rCBF). Compared with MRI, ^{99m}Tc-HMPAO brain images have proven to be more accurate in detecting brain involvement in autoimmune connective tissue disease and to have better correlation with clinical diagnosis (*10–13*).

In this study, we investigated the potential of ^{99m}Tc-HMPAO brain images compared with brain MRI to detect cerebral anomalies, including lesions of the gray and white matter, in BS patients with neuropsychiatric symptoms or signs.

MATERIALS AND METHODS

Patients

Thirteen patients (7 women, 6 men; aged 28–62 yr) with BS were enrolled in this study. The diagnosis of BS was established on the basis of the criteria of the Behçet's Disease Research Committee of Japan (*14*): the presence of a triple-symptom complex, including recurrent aphthous stomatitis, genital ulcers and relapsing uveitis. Besides this triad, additional features, including synovitis, cutaneous vasculitis and meningoencephalitis, are recognized

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