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## $^{99m}$Tc-HMPAO Brain Perfusion Single-Photon Emission Computed Tomography in Children with Down Syndrome: Relationship to Epilepsy, Thyroid Functions, and Congenital Heart Disease

## ABSTRACT

In recent years, it has been possible for patients with Down syndrome to live longer with advanced medical treatment and social support. As a result, the problems of these patients, such as thyroid diseases, leukemia, and Alzheimer disease, would be encountered more frequently. In this study, we aimed to perform the brain perfusion of children with Down syndrome by technetium 99m hexamethylpropylene amine oxime ($^{99m}$Tc-HMPAO) single-photon emission computed tomography (SPECT) and to determine the relationship between brain perfusion and epilepsy, thyroid function tests, congenital heart disease, and level of mental and motor development. Thirty patients with Down syndrome, aged between 1 and 15 years, were included in our study. Demographic data, the existence of epilepsy and congenital heart defects, the level of mental and motor development, serum levels of thyroid hormones, and autoantibodies were determined. All patients underwent computed tomography (CT) and/or magnetic resonance imaging (MRI). Cerebral SPECT was performed in all cases to evaluate the brain perfusion pattern. According to the visual evaluation of cerebral SPECT results, hypoperfusion was detected in 11 cases (37%). Patients with cerebral hypoperfusion (group 1) and patients with normal cerebral perfusion (group 2) were compared. There was no difference between group 1 and group 2 in terms of demographic data, congenital heart defects, IQ levels, thyroid hormones, and autoantibodies, but the incidence of epilepsy was significantly higher in group 1 ($P < .001$). When motor and mental development levels were compared, it was found that cases in group 1 were significantly more retarded in personal-social and fine motor skills ($P < .05$). The present study showed that cerebral hypoperfusion in children with Down syndrome is mostly related to epilepsy and the other coexisting conditions, congenital heart disease and hypothyroidism. Patients with cerebral hypoperfusion also have more retarded developmental levels, especially in personal-social and fine motor skills. (*J Child Neurol* 2006;21:610–614; DOI 10.2310/7010.2006.00144).

Down syndrome is characterized by the typical dysmorphic appearance and moderate mental retardation, in addition to a variety of abnormalities involving multiple organ systems. Congenital heart diseases, hypothyroidism, gastrointestinal malformation, immune system defects, leukemia, and Alzheimer disease–type dementia after the age of 35 years are common in Down syndrome.[1,2] In adult patients with Down syndrome with Alzheimer disease, bilateral brain hypoperfusion was detected by single-photon emission computed tomography (SPECT) studies.[3,4] Similar perfusion defects have also been demonstrated in children with Down syndrome.[5,6]

The aim of this study was to investigate changes in brain perfusion using technetium 99m hexamethylpropylene amine oxime ($^{99m}$Tc-HMPAO) SPECT in children with Down syndrome and to determine the relationship between cerebral hypoperfusion and hypothyroidism, congenital heart disease, epilepsy, and the level of mental and motor development.

### *Material and Methods*

Thirty children with Down syndrome (18 boys, 12 girls), aged 1 to 15 years, were included in this study. The patients, all with regular trisomy, had no history of birth asphyxia. Informed consent was obtained from parents for this investigation, and the Faculty Ethics Committee approved the study. Data relating to age, sex, weight, height, head circumference, the existence of epilepsy or congenital heart disease, and the level of mental and motor development were recorded. If epilepsy was present, it was defined as the occurrence of at least two unprovoked seizures in at least 24 hours.[7] Serum free triiodothyronine, free thyroxine, thyroid-stimulating hormone, and antithyroid peroxidase antibody and antithyroglobulin antibody levels were determined by chemical immunoassay methods (Immulite Diagnostic Products Corporation, Los Angeles, CA). In all patients, computed tomography (CT) and/or magnetic resonance imaging (MRI) performed within 1 week from the SPECT examination did not show focal brain abnormalities, the only pathologic finding being common ischemic changes of the brain in one patient (patient 7). To identify the mental and intellectual capacity of the patients, the Denver Developmental Screening Test was performed in children under 6 years of age. The personal-social, fine motor adaptive, language, and gross motor functions were evaluated with the Denver Developmental Screening Test.[8,9] The Denver Developmental Screening Test results are given in terms of the number of parameters that resulted in failure and the percentage of failures according to age group. IQ scores were performed for patients older than 6 years.

### *SPECT Study*

Before the SPECT study was performed, the patients were placed in a quiet environment, an intravenous line was inserted, and 0.5 mCi/kg (18.5 MBq/kg) of $^{99m}$Tc-HMPAO (maximum 15 mCi) was administered a few minutes later. SPECT was performed within 60 to 90 minutes after intravenous administration of the radiotracer. Either the head or the whole trunk was placed in a polystyrene vacuum cushion, depending on the size of the patient. The acquisition was performed under monitored sedation administered following injection of the tracer. A rotating, large–field of view gamma camera interfaced to a dedicated computer system (Philips Diagnost Tomo, Philips, Eindhoven, the Netherlands) was used. During a 360-degree rotation, a low-energy, high-resolution collimator acquired 64 images with a 128 × 128 matrix. Transaxial slices were obtained parallel to the anterior commissure-posterior commissure line. These slices displayed cerebellar, cerebral cortical, and subcortical lobes. Transaxial, coronal, and sagittal slices were analyzed visually.

### *Visual Evaluation*

Interpretation of the SPECT scans was performed qualitatively by reviewing the images on a computer screen and by one experienced physician who was blind to the clinical, electroencephalographic, and structural imaging data. A region was interpreted to show decreased perfusion if the degree of uptake appeared to be substantially lower than that of adjacent and contralateral areas of the brain.

### *Statistical Analysis*

According to visual analysis, patients were classified as group 1 (patients with hypoperfusion on brain perfusion SPECT) and group 2 (patients with normal brain perfusion SPECT). The existence of thyroid dysfunction, epilepsy, congenital heart defects, and mental and motor deficit was compared between the groups. The Mann-Whitney *U*-test was used to compare the parameters. The results were expressed as mean ± standard

deviation for continuous variables. All calculations were made using *Minitab* Release 13 (Minitab Inc., USA; reference number WCP 1331.00197). $P < .05$ was considered statistically significant.

### Results

The clinical findings and hypoperfused regions on cerebral SPECT of group 1 children are summarized in Table 1. Visual evaluation of the brain SPECT revealed 29 hypoperfused regions in 11 (37%) of 30 patients with Down syndrome. Hypoperfusion was detected in the left hemisphere in 6 (55%) patients and in the right hemisphere in 4 (36%) patients, and in 10 (91%) patients, the hypoperfusion was unilateral (Figure 1). Bilateral hypoperfusion was seen in one (9%) patient. In four (36%) subjects, hypoperfusion was localized to the basal ganglia regions (Figure 2). The clinical findings of group 2 children with normal cerebral perfusion are illustrated in Table 2.

When the results of the groups were evaluated statistically, there was no difference in terms of age, sex, weight, height, head circumference, congenital heart disease, IQ levels, free triiodothyronine, free thyroxine, thyroid-stimulating hormone, and thyroid autoantibody levels. However, the epilepsy incidence was significantly higher in group 1 than group 2 ($P < .001$) (Table 3). We compared developmental levels and found that group 1 was significantly more retarded in personal-social ($P < .05$) and fine motor skills ($P < .05$) (Table 4).

### Discussion

In recent years, satisfactory treatment of cardiac defects, other congenital anomalies, and infectious diseases, in addition to better social support, resulted in increased life expectancy for patients with Down syndrome. Today, as a consequence of increased survival, more patients with Down syndrome are being diagnosed with hypothyroidism, epilepsy, autoimmune diseases, leukemia, and Alzheimer disease.[2] The cause of 85% to 90% of all Down syndrome is a trisomy of chromosome 21. The occurrence of Alzheimer disease in such a high percentage of the subjects with Down syndrome suggests that chromosome 21 genes might be involved in both diseases.[5,10] Evenhuis performed autopsy on 10 cases of Down syndrome: 8 demented patients and 2 nondemented patients.[11] Neuropathologically, Alzheimer-type abnormalities were demonstrated in nine patients, both demented and nondemented. In addition, this study showed that the incidence of epileptic seizures and myoclonus was about eightfold in demented patients with Down syndrome. Schapiro et al reported that healthy young adults with Down syndrome did not have alterations in their regional or global brain metabolism, as measured with [$^{18}$F]fluorodeoxyglucose positron emission tomography (PET), prior to an age at which the Alzheimer disease–type neuropathologic changes occur.[12] Kao et al detected unilateral cerebral hypoperfusion in 14 patients with Down syndrome aged between 8 and 30 years.[5] Similarly, Gökçora et al performed cerebral SPECT studies in 17 young patients with Down syndrome without dementia and showed hypoperfusion in 8 (47%) of them.[6] Perfusion defects were usually unilateral and localized in the frontal, parietotemporal, and parieto-occipital regions. They concluded that those findings might not be considered predictive patterns of dementia related to Alzheimer-type perfusion deficits in Down syndrome.

In our study, cerebral hypoperfusion was shown to be mostly in the unilateral frontal, parietal, temporal, and occipital cerebral cortical regions, confirming the results of previous studies on regional brain perfusion in subjects with Down syndrome.[5,6] There was no difference between involvement of the right or left cerebral hemisphere. We found that cerebral hypoperfusion was significantly related to epilepsy, and these patients also had more retarded developmental levels, especially in personal-social and fine motor skills. In addition to these findings, basal ganglia hypoperfusion was also detected in four patients with Down syndrome. Although we think that basal ganglia hypoperfusion in our patents might be related to epilepsy, an asymmetric blood flow pattern in the basal ganglia on interictal SPECT can be seen in frontal[13] and temporal lobe epilepsy[14] and crossed cerebellar diaschisis in children.[15] These disorders should be kept in mind by evaluation of interictal SPECT in children.

**Table 1. Clinical Findings and Hypoperfused Regions on Cerebral Single-Photon Emission Computed Tomography of Group 1 Children**

| Patient | Sex | Age (yr) | Epilepsy | Epileptic Foci | Heart Disease | Thyroid Disease | IQ Scores | Denver Developmental Screening Test* | | | | Hypoperfused Regions |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | PS | FM | L | GM | |
| 1 | M | 15 | | | ECD | AT | 45 | | | | | Rt, F-P-T |
| 2 | M | 8 | PG | No foci | | | 55 | | | | | Rt, BG |
| 3 | F | 7.5 | | | | | 66 | | | | | Lt, BG |
| 4 | M | 10 | CPE | Lt, P-O | | | 63 | | | | | Lt, P-BG |
| 5 | M | 2 | CPE | Rt, P-O | PVS | | | 6 (50) | 5 (28) | 5 (50) | 8 (42) | Rt, P-T-O |
| 6 | F | 12 | | | | | 65 | | | | | Rt, P-T |
| 7 | M | 5 | SGP | Rt, P-T-O | ECD + ES | | | 12 (75) | 20 (80) | 22 (73) | 18 (69) | Bil, P-T-O-BG |
| 8 | M | 9.5 | | | | | 49 | | | | | Lt P, Rt F |
| 9 | F | 5 | CPE | Lt, P-O | VSD | | | 12 (75) | 21 (84) | 23 (77) | 18 (69) | Lt F-P-T |
| 10 | M | 5.5 | | | | | | 5 (29) | 6 (22) | 6 (20) | 5 (16) | Lt F-P |
| 11 | F | 3.5 | | | | | | 4 (30) | 6 (28) | 4 (17) | 4 (20) | Lt F-P |

AT = autoimmune thyroiditis; BG = basal ganglion; Bil = bilateral; CPE = complex partial epilepsy; ECD = endocardial cushion defects; ES = Eisenmenger syndrome; F = frontal lobe; FM = fine motor; GM = gross motor; L = language; O = occipital lobe; P = parietal lobe; PG = primarily generalized; PS = personal-social; PVS = pulmonary valve stenosis; SGP = secondarily generalized partial epilepsy; T = temporal lobe; VSD = ventricular septal defects.
*The Denver Developmental Screening Test results are given in terms of the number of parameters that resulted in failure and the percentage of failures according to age group.

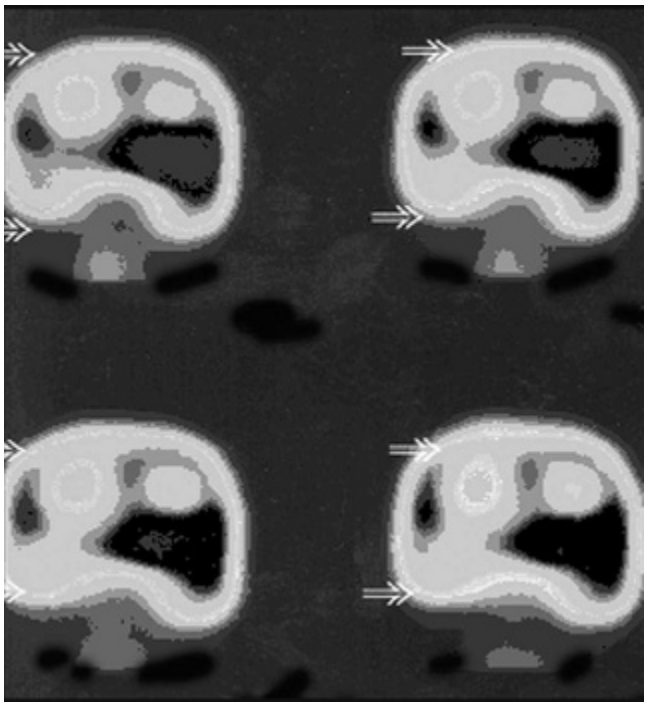

Figure 1. Coronal slices of the $^{99m}$Tc-HMPAO brain single-photon emission computed tomography show right parietal and temporal hypoperfusion in a 15-year-old male with Down syndrome (*arrows* indicate hypoperfusion regions).

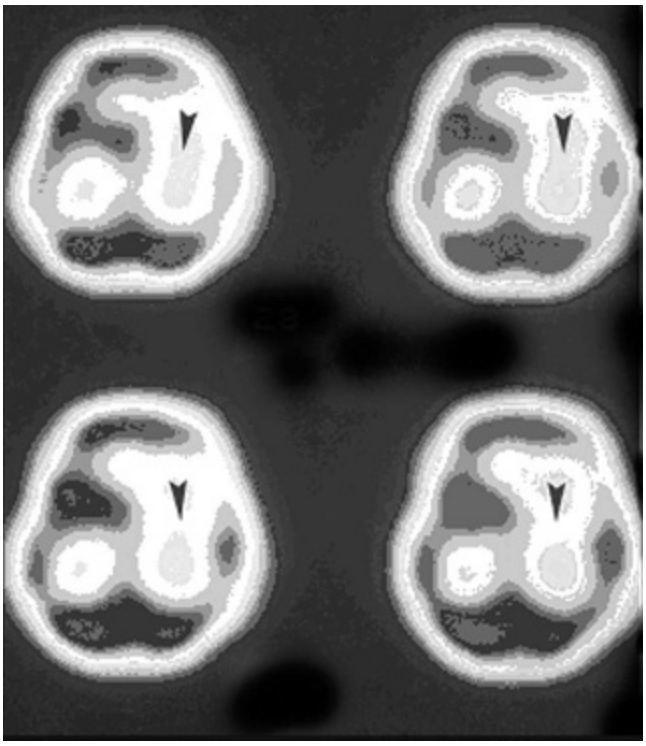

Figure 2. Transaxial slices of the $^{99m}$Tc-HMPAO brain single-photon emission computed tomography shows hypoperfusion on the left basal ganglia in a 7.5-year-old girl with Down syndrome (*arrowheads* indicate hypoperfusion regions).

It is known that thyroid hormone function is essential for normal brain function and development. Hypothyroidism causes global hypoperfusion probably by lowering the metabolism rate in the brain.[16,17] In a case report of Down syndrome, thyroid dysfunction was shown to induce reversible diffuse cerebral hypoperfusion by SPECT.[16] The pattern of hypoperfusion observed was different from that of Alzheimer disease, and the cerebral blood flow normalized when the patient was euthyroid. In our study, the only patient with hypothyroidism owing to autoimmune thyroiditis was not receiving thyroxine therapy because the 15-year-old boy's diagnosis was made during a cerebral SPECT study. This patient's SPECT revealed cerebral perfusion defects. Similarly, Forchetti et al reported bilateral reversible cerebral hypoperfusion in a patient with lowered free thyroxine and elevated thyroid-stimulating hormone levels without symptoms of hypothyroidism caused by Hashimoto thyroiditis.[17] The other four children with Down syndrome with congenital and

**Table 2. Clinical Findings of Group 2 Children With Normal Cerebral Perfusion**

| *Patient* | *Sex* | *Age (yr)* | *Epilepsy* | *Heart Disease* | *Thyroid Disease* | *IQ Scores* | *Denver Developmental Screening Test** | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *PS* | *FM* | *L* | *GM* |
| 1 | M | 12 | | VSD | | 50 | | | | |
| 2 | F | 2.5 | | VSD | | | 0 (0) | 4 (22) | 1 (6) | 1 (5) |
| 3 | M | 5.5 | | | | | 10 (59) | 21 (78) | 25 (83) | 20 (65) |
| 4 | F | 6.5 | | | IET | | 2 (11) | 0 (0) | 9 (27) | 14 (37) |
| 5 | M | 2 | | | | | 1 (8) | 3 (17) | 2 (20) | 2 (10) |
| 6 | F | 1 | | ECD (Op) | | | 2 (25) | 4 (36) | 3 (38) | 5 (45) |
| 7 | M | 3.5 | | | AH | | 2 (15) | 3 (14) | 8 (35) | 4 (20) |
| 8 | M | 4 | | ECD (Op) | | | 2 (13) | 5 (22) | 7 (27) | 6 (26) |
| 9 | F | 4 | | ECD + PDA (Op) | AH | | 2 (13) | 4 (17) | 6 (23) | 6 (26) |
| 10 | F | 3 | | | IET | | 0 (0) | 3 (15) | 7 (37) | 7 (35) |
| 11 | M | 9.5 | | MVP | | 55 | | | | |
| 12 | F | 4.5 | | | | | 2 (13) | 3 (13) | 9 (33) | 6 (26) |
| 13 | F | 11 | | | | 58 | | | | |
| 14 | M | 9 | | | | 60 | | | | |
| 15 | M | 9 | | ASD | | 38 | | | | |
| 16 | M | 5 | | | | | 2 (13) | 5 (20) | 8 (27) | 6 (23) |
| 17 | M | 7 | | | CH | | 1 (6) | 4 (14) | 4 (12) | 3 (8) |
| 18 | M | 10 | | | | 55 | | | | |
| 19 | F | 2.5 | | ASD + VSD (Op) | CH | | 3 (17) | 11 (61) | 7 (44) | 11 (55) |

AH = acquired hypothyroidism; ASD = atrial septal defect; CH = congenital hypothyroidism; ECD = endocardial cushion defects; FM = fine motor; GM = gross motor; IET = isolated elevated thyroid-stimulating hormone; L = language; MVP = mitral valve prolapse; Op = operated; PDA = patent ductus arteriosus; PS = personal-social; VSD = ventricular septal defect.

*The Denver Developmental Screening Test results are given in terms of the number of parameters that resulted in failure and the percentage of failures according to age group.

**Table 3. Comparison of Groups 1 and 2 With Respect to Demographic Data, Body Size, Existence of Epilepsy, Congestive Heart Disease, and Thyroid Disease**

| *Patient Characteristics* | *Group 1 (n = 11)* | *Group 2 (n = 19)* | P |
|---|---|---|---|
| Sex (F/M), *n* (%) | 4 (36)/7 (64) | 8 (42)/11 (58) | NS |
| Age (yr) | 7.5 ± 3.9 (7.5 [2.0–15.0]) | 5.9 ± 3.3 (5.0 [1.0–12.0]) | NS |
| Weight (kg) | 22.1 ± 11.8 (19.0 [7.8–46.0]) | 16.3 ± 7.2 (15.0 [7.0–35.0]) | NS |
| Length (cm) | 112.4 ± 22.8 (113.0 [83.0–54.0]) | 98.5 ± 18.1 (94.0 [63.0–132.0]) | NS |
| Head circumference (cm) | 47.2 ± 2.9 (48.0 [40.2–51.0]) | 46.9 ± 2.2 (47.0 [42.5–52.0]) | NS |
| Epilepsy, *n* (%) | 5 (46) | 0 | < .001 |
| CHD, *n* (%) | 4 (36) | 8 (42) | NS |
| Thyroid disease, *n* (%) | 1 (9) | 6 (32) | NS |
| CH | 0 | 2 | |
| AH | 0 | 2 | |
| IET | 0 | 2 | |
| AT | 1 | 0 | |

AH = acquired hypothyroidism; AT = autoimmune thyroiditis; CH = congenital hypothyroidism; CHD = congestive heart disease; IET = isolated elevated thyroid-stimulating hormone; NS = not significant.
Mean ± SD (median [minimum–maximum]).

**Table 4. Comparison of Groups 1 and 2 With Respect to IQ Scores and Denver Development Screening Test (DDST) Results**

| *DDST* | *Group 1 (n = 11)* | *Group 2 (n = 19)* | P |
|---|---|---|---|
| IQ scores | 57.2 ± 8.9 (59.0 [45.0–66.0]) | 52.7 ± 7.9 (55.0 [38.0–60.0]) | NS |
| PS (%) | 51.80 ± 22.77 (50.0 [29.0–75.0]) | 14.84 ± 14.86 (13.0 [0.0–59.0]) | < .05 |
| FM (%) | 48.40 ± 30.80 (28.0 [22.0–84.0]) | 25.30 ± 21.42 (17.0 [0.0–78.0]) | < .05 |
| L (%) | 47.40 ± 28.34 (50.0 [17.0–77.0]) | 31.69 ± 18.69 (27.0 [6.0–83.0]) | NS |
| GM (%) | 43.20 ± 25.54 (42.0 [16.0–69.0]) | 29.30 ± 17.90 (26.0 [5.0–65.0]) | NS |

FM = fine motor; GM = gross motor; L = language; NS = not significant; PS = personal-social.
Mean ± standard deviation (median [minimum–maximum]).

acquired hypothyroidism did not show any abnormalities on regional cerebral perfusion SPECT. We think that this is related to thyroxine replacement therapy. Two of the children with Down syndrome had only isolated elevated thyroid-stimulating hormone, and they showed normal regional cerebral perfusion on SPECT.

Cerebral hypoperfusion was reported in patients with congenital heart disease caused by cerebral emboli.[18] In the present study, we did not find a statistical difference between group 1 and group 2 with respect to congenital heart disease. However, four patients with Down syndrome with congenital heart disease showed various types of cerebral perfusion defect on SPECT. In general, the endocardial cushion defect is the most frequent congenital heart disease in Down syndrome.[3] This cardiac defect, also known as Eisenmenger syndrome, can easily lead to right to left shunt. Cerebral thrombosis owing to hyperviscosity and right to left shunt is common in Eisenmenger syndrome. We also detected bilateral parietal, temporal, occipital, and basal ganglia hypoperfusion in a 5-year-old boy (patient 7) who had Eisenmenger syndrome owing to a severe, untreated endocardial cushion defect. He also showed common ischemic changes on brain CT.

In this study, cerebral hypoperfusion assessed by SPECT was found in nearly one third of the children with Down syndrome. When mental and motor achievements were compared between groups, patients with cerebral hypoperfusion were found to have lower scores in personal-social and fine motor areas. The probable cause of hypoperfusion in our study was coexisting conditions such as epilepsy, congenital heart disease, and hypothyroidism. In the present study, epilepsy was the most relevant factor with cerebral hypoperfusion. $^{99m}$Tc-HMPAO brain SPECT showed interictal hypoperfusion on the side of the epileptic focus.[19,20] Epileptic seizures are reported to occur in less than 9% of patients with Down syndrome.[3,21] But in this study, we found that 17% of the children with Down syndrome had epilepsy and all had SPECT abnormalities. One of the methodologic limitations in our study is a lack of quantitative assessment of SPECT images. However, in visual analysis, comparison on transaxial, coronal, and sagittal slices of SPECT images was performed not only with the other hemisphere but also with neighboring regions.

In conclusion, the present study showed that regional cerebral hypoperfusion on $^{99m}$Tc-HMPAO SPECT in children with Down syndrome was mostly related to epilepsy and the other coexisting conditions of congenital heart disease and hypothyroidism. In addition, the children with regional cerebral hypoperfusion also had more retarded developmental levels, especially in personal-social and fine motor skills, than children with normal cerebral perfusion.

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## Neuroradiologic Findings in Sotos Syndrome


### ABSTRACT

Sotos syndrome is a well-known anomaly syndrome characterized by overgrowth, characteristic facial gestalt, and developmental delay, and haploinsufficiency of the *NSD1* gene has been revealed as one of the major genetic causes. However, there have been only a few reports on neuroradiologic findings by computed tomography (CT) or magnetic resonance imaging (MRI), and functional examination of the brain has not been reported. We examined three cases with typical Sotos syndrome, which also were confirmed by genetic analysis with a specific probe for the *NSD1* gene. The results of MRI showed the characteristic features that have been reported previously. The findings obtained by using single-photon emission computed tomography and magnetic resonance spectroscopy suggested an association between mental delay and behavioral tendency in Sotos syndrome and immaturity in frontal brain function. (*J Child Neurol* 2006;21:614–618; DOI 10.2310/7010.2006.00145).


Sotos syndrome is an anomaly syndrome characterized by overgrowth, characteristic facial gestalt, and developmental delay.[1,2] Recently, haploinsufficiency of the *NSD1* gene was revealed as one of the major genetic causes of Sotos syndrome.[3] From the first report by Sotos et al, more than 200 cases have been reported to date, but there have been only a few reports on neuroradiologic findings by computed tomography (CT) or magnetic resonance imaging (MRI).[1,4,5] Moreover, functional examination by using single-photon emission computed tomography (SPECT) or magnetic resonance spectroscopy has not been reported. We report here the neuroradiologic findings of three patients with Sotos syndrome examined by MRI, SPECT, and magnetic resonance spectroscopy, suggesting an immaturity in frontal brain function.

### *Case Reports*

#### *Case 1*

A 3.5-year-old boy was referred for evaluation of his large body size and slow mental and motor development. His height and weight were around the +5 SD line but parallel with the average growth line. The pregnancy was uneventful, and he was born at 38 weeks with mild asphyxia and had moderate jaundice requiring phototherapy. His weight at birth was 4006 g (+2.0 SD), but data regarding his height and head circumference at birth were not obtained. He showed poor sucking ability owing to a cleft palate and remained in hospital until 45 days of age. Further, he could not hold his head up until 10 months. There was no family history of mental deficiency or gigantism. On examination, his height was 119 cm (+5.4 SD), equal to that of an average 7-year-old boy. He had a dolichocephalic head, which measured 57.5 cm (+5.0 SD), and there was frontal bossing and a prominent jaw. The cleft palate had been operated on. His eyes were widely spaced, and his hands and feet were large. His bone age was as advanced as that of a 7-year-old child. Eye funduscopic examination revealed no abnormal findings. He could sit but could not stand without help. He was unable to speak any significant words, and his developmental quotient, evaluated by the Enjouji Developmental Scale for Japanese children, was 34. He demonstrated significant instability of temper and was aggressive toward other people. The aggressiveness was triggered when he was contradicted. He frequently hit his own head on the floor.

#### *Case 2*

A 2-year-old boy was referred for evaluation of his slow mental and motor development. His height and weight were around the +2 SD line but parallel with the average growth line. The pregnancy had been uneventful, but he was born at 41 weeks by ceasarean section owing to his fetal asphyxia. His weight, height, and head circumference at birth were 4080 g (+2.2 SD), 53.5 cm (+1.5 SD), and 36.0 cm (+1.6 SD), respectively. He had mild jaundice that did not require phototherapy. He was unable to hold his head up until 5 months, and at 11 months, he still could not sit alone. At 18 months of age, he became able to walk unaided. There was no family history of mental deficiency or gigantism. On examination, his height was 90.8 cm (+2.0 SD), equal to that of an average