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Perfusion Impairment in Infantile Autism on Brain SPECT Using Tc-99m ECD : Comparison with MR Findings

Division of Nuclear Medicine, Department of Diagnostic Radiology, Department of Psychiatry, Yonsei University College of Medicine, Department of Diagnostic Radiology**, Poondang Cha General Hospital, Seoul, Korea

Young Hoon Ryu, M.D., **Jong Doo Lee**, M.D., **Pyeong Ho Yoon**, M.D.
Dong Ik Kim, M.D., **Young Taik Oh**, M.D., **Sunah Lee**, M.D.
Ho Bun Lee, M.D.*, **Yee Jin Shin**, M.D.* and **Byung Hee Lee**, M.D.**

= 국문 초록 =

유아 자폐증 환아에서의 Tc-99m ECD를 이용한 뇌 단일 광전자 방출 전산화 단층 촬영술상의 관류 저하: 자기 공명 영상과의 비교 분석

연세대학교 의과대학 진단방사선과학교실 핵의학과, 정신과학교실*, 분당 차병원 진단방사선과**

유영훈 · 이종두 · 윤평호 · 김동익 · 오영택 · 이선아 · 이호분* · 신의진* · 이병희**

유아 자폐증 환아에서의 신경 방사선학적 소견은 계속 연구되어 왔으나 이전의 연구에서는 일관된 특징적인 소견을 보여주지 못하였고, 대부분의 연구에서 성인이나 학령기 아동을 대상으로 하였었다. 본 연구는 8세 이전의 환아만을 대상으로 자기공명영상과 뇌혈류 SPECT의 기능적, 해부학적 이상을 알아보고자 하였다.

DSM-IV와 CARS의 진단기준을 만족하는 18명의 환아를 대상으로 후향적으로 뇌혈류 SPECT와 자기공명영상 소견을 분석하였다. 환아의 평균연령은 55개월(28-89 개월)이었다. SPECT는 185-370 MBq의 Tc-99m ECD를 정맥주사후 annular crystal 감마카메라를 이용하여 시행하였고 자기공명영상은 1.5 Tesla GE signa machine을 이용하여 T1,T2 axial과 T1 sagittal sequence를 얻었다.

뇌혈류 SPECT 상 13명의 환아에서 국소적인 관류저하가 관찰되었고 각각 소뇌 충부(12/18), 소뇌반구(11/18), 시상(13/18), 기저핵(4/18), 두정엽(7/18), 측두엽(1/18)에서 관류저하 소견을 보였다. 반면 자기공명영상에서는 3명의 환아에서만 이상 소견을 보였는데 각각 뇌실 주변부 백질의 감소(3/18), 뇌량의 간 및 팽대부의 위축(1/18), 소뇌 충부의 용적 감소 (1/18)를 보였다. 뇌혈류 SPECT와 자기공명영상에서 나타난 이상 소견을 비교하여 볼 때 자기공명영상상의 합당한 해부학적 이상 소견이 없음에도 뇌혈류 SPECT에서 더 광범위한 혈류 저하 부위를 보였다.

결론적으로 뇌혈류 SPECT상 광범위한 관류 저하를 소뇌, 시상, 두정엽에서 관찰할 수 있었고, 뇌혈류 SPECT가 자기공명영상에 비하여 유아 자폐증의 병태생리를 반영함에 있어 더 민감한 방법임을 알 수 있었다. 하지만 시상이나 두정엽의 관류 저하의 임상적 의미에 관한 더 많은 연구가 필요할 것으로 생각한다.

Send correspondence to Young Hoon Ryu, M.D.: Division of Nuclear Medicine, Department of Diagnostic Radiology Yonsei University College of Medicine Seodaemoon-Gu Shinchon Dong 134, Seoul, Korea
Tel : 82-2-361-5837 Fax : 82-2-393-3035
E-mail : ryuyh@yumc.yonsei.ac.kr

INTRODUCTION

Infantile autism is a neurologic disorder of unknown and possible heterogeneous etiologies

that was first described by Kanner. It severely disrupts the development of many higher cognitive functions[1, 2]. The essential features of autistic disorder are the presence of markedly abnormal or impaired development in social interaction and communication, and a markedly restricted repertoire of activity and interests[3].

Neuroanatomic substrate of autism has been the subject of continuing investigation. One of the most frequently found abnormalities in autism with or without mental retardation is a reduction of cerebellar tissue, and which appears to be greatest in neocerebellar regions within the vermis and hemispheres[4-10]. Various regional cortical abnormalities have been described although no consistent cortical abnormalities have yet been found[11, 12]. Subtle abnormalities of the parietal lobe are described by Courchesne and colleagues[11] and cortical malformation such as polymicrogyria, schizencephaly and macrogyria are reported by Piven et al[12]. However, none of the findings fully account for the clinical expression of autism.

Functional brain imaging studies with positron emission tomography (PET) or single photon emission computed tomography (SPECT) have failed to detect consistent focal abnormalities in autistic adults and school-aged autistic patients [13-20]. George et al found clear-cut frontal and temporal hypoperfusion in an autistic subject using Tc-99m-hexamethyl propyleneamine oxime (HMPAO) SPECT[13]. Mountz et al. suggested that temporal and parietal lobes had abnormal regional cerebral blood flow (rCBF) [14]. Schifter et al reported 6 out of 13 mentally retarded autistic children had regional abnormalities especially in the parietal, occipital and temporal areas using F-18 fluorodeoxyglucose (FDG) with PET[15]. However, alterations in cerebellar blood flow or metabolism have not yet been detected in autism[15, 16].

Because previous studies had not demonstrated consistent and specific neuroimaging findings in autism and most studies comprised adult and school-age children autistic subjects, we performed a retrospective review of 18 children who were diagnosed as autism in search of common functional and anatomical abnormalities with SPECT imaging using technetium-99m-ethyl cysteinate dimer (ECD) and correlative magnetic resonance imaging (MRI).

PATIENTS AND METHODS

The patient population was composed of 18 children aged 28 to 89 months (15 boys and 3 girls; mean age, 55 months). Patients were clinically evaluated by pediatric psychiatrists (H.B.L and Y.J.S). The diagnosis of autism was made conservatively; only patients who met the diagnostic criteria of autism as defined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and the Childhood Autism Rating Scale (CARS) were included[3, 21]. No patients with Asperger's syndrome or nonautistic pervasive developmental delay were included. No autistic subjects had other significant medical condition or a neurological disorder, including seizures, by history or on examination. None of these autistic patients were known to have fragile X syndrome. Only one patient had a perinatal asphyxia history due to prolonged labor. Clinical data including CARS and social quotient (S.Q) are summarized in Table 1. Before SPECT imaging, the nature of the study procedure was fully explained to parents or legal guardian of each subject, and informed consent was obtained.

1. SPECT Imaging

After an intravenous injection of 185 to

Table 1. Summary of Clinical Data and Neuroimaging Findings

No	Age/Sex	S.Q	CARS	SPECT								MR
	(months)			Cbll	vermis	BG	Tha	Temp	Pari	Fron	Occi	
1	78/M	48	36.54	N	N	N	N	N	N	N	N	N
2	72/M	67	33	N	N	N	B	N	N	N	N	N
3	28/M	76	28	N	N	N	N	N	N	N	N	N
4	38/M	55	35.5	B	D	L	B	L	L	N	N	N
5	85/M	94	27	N	N	N	N	N	N	N	N	N
6	67/M	49	39.5	N	N	N	N	N	N	N	N	N
7	41/M	58	41.5	B	D	N	L	N	L	N	N	P-OWN, C.C, VERM
8	27/M	84	30.5	N	N	N	N	N	N	N	N	N
9	34/M	84	28	B	D	N	B	N	N	N	N	N
10	35/M	98	31	B	D	N	B	L	L	N	N	P-O WM, C.C
11	87/M	89	32	B	D	B	B	N	N	N	N	N
12	89/M	81	38	B	N	N	B	L	N	N	N	N
13	32/M	67	30	B	D	B	B	N	L	N	N	N
14	46/M	74	29	B	D	N	B	N	L	N	N	N
15	41/M	72	29.5	B	D	N	B	B	L	N	N	P-OWM
16	54/M	75	30	B	D	N	B	N	L	N	N	N
17	89/M	82	36	B	D	N	B	N	N	N	N	N
18	47/M	66	37	B	D	L	B	N	N	N	N	N

Abbreviations-No : patient number, S.Q : Social Quotient, CARS : Childhood Autism Rating Scale, Cbll : Cerebellum, BG : Basal Ganglia, Thal : Thalamus, Temp : Temporal lobe, Pari : Parietal lobe, Fron : Frontal lobe, Occi : Occipital lobe, N : Normal, D : Decreased B : Bilateral decreased, R : Decreased in right, L : Decreased in left, P-O WM : parieto-occipital white matter volume loss, C.C : corpus callosum posterior body thinning, Verm : subtle vermian hypoplasia

370MBq Tc-99m-ECD, SPECT images were obtained with a brain dedicated annular crystal gamma camera (Digital Scintigraphic Inc, Waltham, USA) equipped with low-energy, high-resolution parallel hole collimators. One hundred twenty projections were acquired using a 128×128 matrix size for 30 minutes. Transaxial images were obtained by the filtered back projection method using a Butterworth filter (Nyquist frequency; 1.1cycle/cm). Attenuation correction of the transaxial images were performed by Chang's method, and coronal and sagittal slices were calculated from the original transaxial images (parallel to the orbitomeatal line). Patients were sedated by intramuscular injection of 1.6mg/kg of chlorpromazine for the acquisition of SPECT and MR imaging because they were unable to remain still.

2. MR Imaging

MR imaging was performed with a 1.5 Tesla signa unit (General Electrics Medical Systems, Milwaukee, Wis.). A multisection T2 weighted spin echo (SE) sequence (3333/114 [TR/effective TE], 20cm field of view, 256×256matrix, one excitation) was used to obtain axial images. A multisection T1 weighted sequence (400/12, 20 cm field of view, 256×256 matrix, two excitations) was used to obtain sagittal images centered at midline. Sections were 5mm thick with a 2.5mm interslice gap between adjacent sections. Eleven patients received 0.2mmol/kg of intravenous contrast (Magnevist; Schering, Berlin, Germany).

3. Analysis of SPECT and MRI

All SPECT scans were visually assessed by two nuclear medicine specialists (Y.H.R and J.D.L) who were unaware of clinical history or the results of correlative MRI. An overall qualitative visual grading of the SPECT data by mutual consensus was recorded. Seven bilateral brain areas including frontal, temporal, parietal, occipital cortex, basal ganglia, thalami, cerebellar hemisphere and cerebellar vermis were visually graded as based on a scale of 0 to 2 (0=reduced, 1=normal, 2=increased).

All MRI data were evaluated by two neuroradiologists (D.I.K and B.H.L) who were blinded to clinical history or the results of the SPECT studies. An overall grading of the structural imaging study was recorded and if the study was considered abnormal, the specific anatomic abnormality was recorded. For this study, MRI was reinterpreted with the SPECT data and particular attention was paid to midline cerebellum, fourth ventricle, limbic system, corpus callosum and evaluation of brain asymmetry and of presence of cortical malformation.

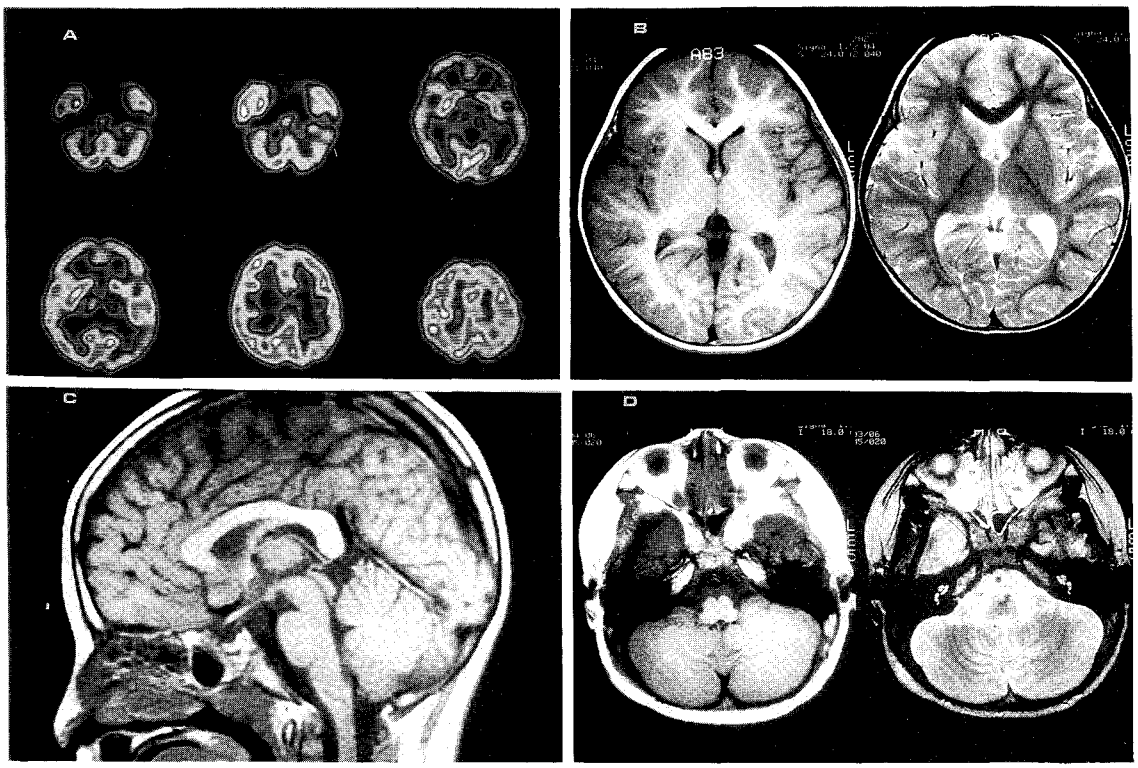

Fig. 1. Case 4. 38 month-old male patient.
a) Transaxial reconstructed SPECT showed decreased perfusion of cerebellar hemisphere, cerebellar vermis, bilateral thalami and left basal ganglia and slightly decreased perfusion of left parietal area.
b) Axial T1(left)- and T2(right)-weighted MR images at the level of basal ganglia and thalamus revealed no visually detectable structural abnormalities.
c) Sagittal T1 weighted and d) Axial T1(left)- and T2(right)-weighted MR images showed normal morphology and signal intensity of the cerebellar vermis and hemispheres.

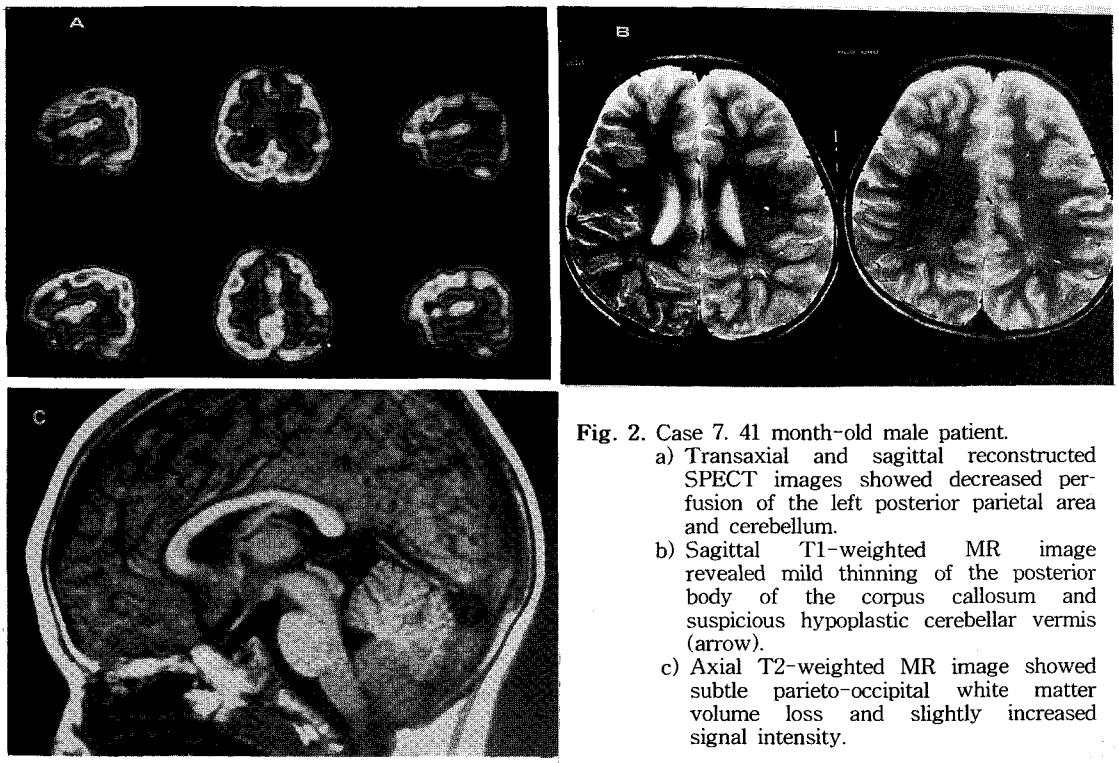

Fig. 2. Case 7. 41 month-old male patient.
a) Transaxial and sagittal reconstructed SPECT images showed decreased perfusion of the left posterior parietal area and cerebellum.
b) Sagittal T1-weighted MR image revealed mild thinning of the posterior body of the corpus callosum and suspicious hypoplastic cerebellar vermis (arrow).
c) Axial T2-weighted MR image showed subtle parieto-occipital white matter volume loss and slightly increased signal intensity.

RESULTS

Thirteen of the eighteen patients had abnormal SPECT scan revealing focal areas of decreased perfusion (Fig. 1 and Fig. 2). Cerebellar vermis and hemisphere showed decreased perfusion in 11 and 12 patients, respectively. Thalamus also showed marked alteration of perfusion; bilaterally decreased perfusion in 12 patients, decreased on left thalamus in 1 patient. Basal ganglia revealed decreased perfusion in 2 patients bilaterally and in 2 patients on left side. Cortical rCBF abnormalities were marked in parietal and temporal areas. Seven patients demonstrated decreased perfusion of left parietal area. Temporal lobe perfusion was normal in 14 patients whereas decreased bilaterally in 1 patients, decreased on left in 3. Frontal lobe and occipital lobe were normal in all patients. Detailed SPECT findings are also summarized in Table 1.

Only three patients had abnormal MR findings. MR studies of these patients revealed subtle parieto-occipital white matter volume loss (Fig. 3) and increased T2 signal intensity in three patients and mild thinning of posterior body of corpus callosum in two patients and slighthy decreased volume of cerebellar vermis in one patient. No contrast enhancing abnormal lesion were present in those patients who received intravenous contrast. No abnormal cortical malformation was noted in all patients.

Comparison of the numbers of abnormal findings revealed that rCBF abnormalities seen on SPECT were more numerous than anatomical abnormalities seen on MRI; i.e., for a given subject, more brain regions revealed rCBF

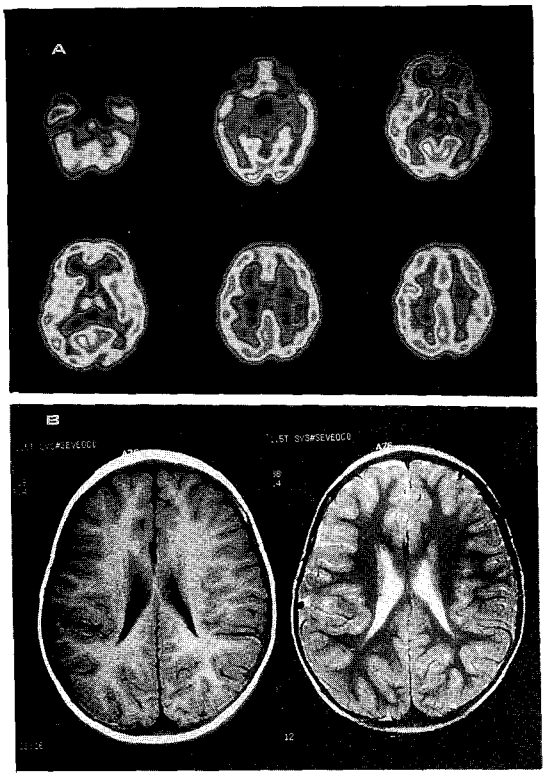

Fig. 3. Case 10. 35 month-old male patient.
a) Transaxial reconstructed SPECT images revealed decreased perfusion of cerebellar hemisphere and vermis, bilateral thalami and left temporal area.
b) Axial T1 (left)- and T2 (right)-weighted MR images revealed parieto-occipital white matter volume loss and wavy appearance of posterior horn of lateral ventricle, bilaterally (arrows).

abnormalities without corresponding anatomic abnormalities.

DISCUSSION

Autism is particularly interesting and significant clinical syndrome for neuroscience, because it is defined by abnormalities in those abilities that most distinguish humans from animals, that is, social and nonsocial behavior, language and cognition. It is now generally considered to be the result of an abnormalities of brain development, although the location and nature of neuropathology responsible for the clinical manifestations are unknown[22, 23].

In pathologic studies of brain specimens of autistic patients, abnormalities have been found in the neocerebellum in all cases studied. In most, but not all, cases studied, abnormalities have also been found in portions of the limbic system. Atrophy of the neocerebellar cortex was accompanied by decreased numbers of Purkinje cells and there was also a decreased number of granular cells[23-26].

Cerebellum may be a common site of developmental abnormalities due to its protracted course of maturation. Recent studies have implicated morphological deviation of the cerebellum as responsible for specific behavioral and cognitive manifestations of autism. Courchesne and colleagues introduced the hypothesis that cerebellar damage might be a common feature in autism, and in 1988, they first reported quantitative MRI evidence of hypoplasia in vermian lobules VI and VII in a group of autistic patients[27]. In 1994, Courchesne et al reported that when all MRI data that they examined from independent samples of autistic patients from independent laboratories are analyzed together, there is highly significant statistical evidence of hypoplasia of vermian lobules VI and VII in the autistic patients[9]. The great majorities of autistic patients fall at or below normal in the size of vermian lobules VI and VII. They reported presence of a second hyperplasia peak that falls far above normal average, consisting of a small percentage of autistic patients[6].

In agreement of previous neuroanatomic studies, our SPECT study revealed prominent decreased perfusion of cerebellar hemisphere and vermis. Up to now, the majority of functional imaging study using PET and SPECT have found no abnormality in cerebellum[13-20]. How-

ever, in our review of MRI, only one case showed suspected cerebellar hypoplasia, and remaining 17 patients showed no visually detectable abnormalities in cerebellum. We recently reported a similar discrepancy in MRI and SPECT findings in the cerebellum in cerebral palsy patient. Those patients who had perinatal asphyxia showed decreased perfusion in cerebellum on SPECT using Tc-99m ECD, whereas MRI revealed no perceptible abnormal signal intensity changes or alteration of cerebellar morphology[28]. In a previous report of Barkovich and Sargent, they stated that MR imaging may not be very sensitive to injury of the cerebellar cortex. The autopsy of one patient in their paper showed extensive neuronal loss and no recognizable external granular layer, Purkinje cell layer, or internal granular layer of the cerebellum, however, cerebellar vermis and hemispheres appeared to have normal shape and signal characteristics[29]. Moreover, it is well known from autopsy and experimental studies that the Purkinje cells of the cerebellar cortex are very vulnerable to hypoxic-ischemic insults [30].

Functional and structural imaging modalities have been combined in a small number of autistic subjects to help localize regions of cortical abnormality such as neuronal migration abnormalities[15]. Diffuse regional cortical abnormalities in rCBF and metabolism have been reported using SPECT and PET[13-20]. Recently, Tc-99m HMPAO SPECT revealed abnormal rCBF in temporal and parietal lobes[16], and in temporal and frontal lobes[13]. PET studies have had conflicting results, with some researchers finding a global increase in cortical metabolism [17, 19], and others not[18]. Some PET study found impaired interaction between frontal/parietal regions and neostriatum and thalamus in autistic patients[19]. In our study, decreased rCBF was demonstrated especially in the thalami and basal ganglia without corresponding regional structural and signal intensity changes on MRI. However, clinical significance of decreased rCBF in the thalami and basal ganglia is uncertain. Bushsbaum et al presented that decreased relative glucose metabolic rate in thalamus and putamen in two of seven autistic patients using FDG-PET and these findings may be consistent with Ornitz' theory of the pathophysiology of autism which emphasizes brain stem and thalamic regions[31, 32]. However, no other PET or SPECT studies concerned the alteration of thalami, up to now. The spatial resolution of SPECT imaging reported in most studies were poorer than 12mm at FWHM but the spatial resolution of current SPECT instrument improved to be in the range of 6 to 7mm (FWHM) in air, therefore this could explain the better visualization of thalamic hypoperfusion in our study. Another possible mechanism for the thalamic hypoperfusion is corticothalamic diaschisis. In patients with decreased perfusion in parietal or frontal or temporal lobes on SPECT study also showed thalamic hypoperfusion in this study. Another possible explanation for the thalamic hypoperfusion is delayed maturation. Recently rCBF in each of the autistic children was measured with SPECT twice during their development: at the age of 3-4 years and 3 years later. A transient frontal hypoperfusion was found in the autistic children at ages 3-4 years; this corresponded to the pattern of perfusion observed in much younger normal children. By the ages of 6-7, the autistic children's frontal perfusion has attained normal values. rCBF pattern in children are related to maturational changes in brain function, these results indicate a delayed frontal maturation in childhood autism. Such a delayed brain maturational process is consistent with the clinical data and cognitive

performance of autistic children[33]. Therefore, follow-up study of our patients will aid in the differentiation of thalamic hypoperfusion might be delayed maturation or true pathologic condition.

Although microscopic analyses of autopsy specimens have suggested a normal cerebrum in autistic patients, Courchesne et al. suggested that visually detectable parietal lobe abnormalities were found in many patients and evidence was found of a reduced size of the corpus callosum in autistic patients[6]. This reduction was localized to posterior regions, where parietal lobe fibers were known to project. In our study, left parietal lobe hypoperfusion is relatively frequently seen (7/18) although no corresponding morphologic changes are noted on MRI. Abnormal regional structural changes seen on MRI are mild diffuse parieto-occipital white matter volume loss and thinning of posterior body of corpus callosum. Parieto-occipital white matter volume loss reflects perinatal hypoxic-ischemic insults. Hypoxic-ischemic encephalopathy in the premature neonate can lead to periventricular leukomalacia, in which there is white matter volume loss in posterior regions and ventriculomegaly and thinning of posterior body of corpus callosum[34]. One of our autistic patients, who may have had perinatal asphyxia during birth due to prolonged labor, had both of the morphologic characteristics of periventricular leukomalacia, but to a very much milder degree than seen in typical cases of periventricular leukomalacia. In very mild cases of periventricular leukomalacia, detected morphological and signal intensity abnormalities may be correspondingly very mild[35].

Like most behaviorally defined syndromes, autism is a heterogeneous disease entity containing different clinical subgroups, which do not manifest similar radiologic features. One limitation of this study is the small sample size, which, in the study of an etiologically heterogeneous disorder such as autism, limits the generalizability of results. And our study does not include a control group of age matched children. At our institution, it is not possible to study ethically normal children as volunteers when radiation exposure is involved. The absence of healthy controls is currently the most important limitation.

In conclusion, more extensive altered cerebral regional blood flow involving cerebellum, thalamus and parietal area were found in this study. SPECT may be more sensitive in reflecting pathophysiology of autism than MRI. And the higher resolution of the brain-dedicated gamma camera may be one reason for the improved detection of abnormalities compared with previous SPECT studies of autism. Further studies are mandatory to determine the significance of thalamic and parietal hypoperfusion.

SUMMARY

Neuroanatomic substrate of autism has been the subjects of continuing investigation. Because previous studies had not demonstrated consistent and specific neuroimaging findings in autism and most studies comprised adults and school-aged children, we performed a retrospective review in search of common functional and anatomical abnormalities with brain SPECT using Tc-99m ECD and correlative MRI.

The patient population was composed of 18 children aged 28 to 89 months(mean age : 55 months) who met the diagnostic criteria of autism as defined in the DSM-IV and CARS. Brain SPECT was performed after intravenous injection of 185-370MBq of Tc-99m ECD using brain dedicated annular crystal gamma camera. MRI was performed in all patients including T1,

T2 axial and T1 sagittal sequences. SPECT data were visually assessed.

Thirteen patients had abnormal SPECT scan revealing focal areas of decreased perfusion. Decreased perfusion of cerebellar vermis(12/18), cerebellar hemisphere(11/18), thalami(13/18), basal ganglia(4/18), posterior parietal(7/18), and temporal(4/18) area were noted on brain SPECT. Whereas, only 3 patients had abnormal MR findings which were subtle volume loss of parieto-occipital white matter in 3 and mild thinning of posterior body of corpus callosum in 2 and slightly decreased volume of cerebellar vermis in 1. Comparison of the numbers of abnormal findings revealed that regional cerebral blood flow (rCBF) abnormalities seen on SPECT were more numerous than anatomical abnormalities seen on MRI.

In conclusion, extensive perfusion impairment involving cerebellum, thalami and parietal lobe were found in this study. SPECT may be more sensitive in reflecting pathophysiology of autism than MRI. However, further studies are mandatory to determine the significance of thalamic and parietal perfusion impairment in autism.

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