Single Photon Emission Computerized Tomography in Children with Developmental Language Disorder – A Preliminary Report

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Developmental language disorder (DLD) is a diagnosis given to a nonautistic child who has inadequate language acquisition despite adequate hearing, sensorimotor, and cognitive skills. We used high-resolution single photon emission computerized tomography (SPECT) with labeled technetium-99m-D, L-hexamethyl-propylene amine oxime (^{99m}Tc-HMPAO) to measure regional cerebral blood flow (rCBF) in 11 children with DLD. Their mean age was 5 years 10 months (range, 4 yr 2 mo to 10 yr 9 mo) and mean nonverbal IQ was 107 (range, 82–137). When inter-hemispheric flow discrepancy was defined as a bilateral rCBF difference of more than 10%, 10 children (90.9%) had discrepant blood flow. Temporal lobes were involved in all 10 children: lateral-temporal in five, medial-temporal in four, and mesial-temporal in four. Though the study was small and the results are preliminary, results suggest that DLD may be a consequence of an underlying neurobiologic problem in areas of the brain known to be involved with language.

Key Words: developmental language disorder, SPECT
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Developmental language disorder (DLD) is a diagnosis given to a nonautistic child who has normal nonverbal intelligence and physical and perceptual abilities but displays failure in normal language development. While some investigators have used the terms specific language impairment, developmental dysphasia, or developmental aphasia, DLD may be a more appropriate term because it emphasizes the developmental, rather than the acquired, nature of the language deficit. In current practice, this clinical label is used when there is inadequate acquisition of one or more aspects of a child's language despite adequate hearing and sensorimotor and cognitive skills [1, 2]. This is a diagnosis of exclusion, rather than one based on the characteristics of the child's language alone. Clinicians mostly regard DLD as a broad range of language disorders and classify these children into qualitatively distinct syndromes such as mixed (receptive/expressive), expressive, and higher order processing subtypes. However, not all clinical classifications have yet been validated statistically [3].

The etiology of DLD is not acquired damage to the immature brain nor the outcome of an unfavorable social environment. Currently, the cause of DLD is thought to be early genetic effects on the structural development of the brain, and the outcome is determined by the combined effect of genetic and environmental influences [4]. In the past, evidence for a neurologic basis of DLD was mostly correlational or behavioral-psychometric, but recent studies provide increasing evidence that DLD is associated with both

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abnormal cerebral lateralization patterns and neurologic pathology at the cellular level [5, 6]. Despite the widely held belief that DLD is caused by neurologic dysfunction, the exact neural pathogenesis has not been proven.

Regional cerebral blood flow (rCBF), which is thought to reflect brain activity, can be measured to study cortical function and to investigate brain function and pathology in the pediatric population [7]. In this study, we used high-resolution single photon emission computerized tomography (SPECT) to measure rCBF in children with DLD. We tested the hypothesis that DLD was a biologic condition caused by brain dysfunction and we tried to identify regional anomalies.

Materials and Methods

Study group

Subjects were recruited from patients at a University Hospital clinic for children with developmental delay. DLD was diagnosed using the following criteria: a performance intelligence quotient (PIQ) of at least 80 on the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), or the Wechsler Intelligence Scale for Children-III (WISC-III) [8, 9], or the Leiter International Performance Scale-Revised [10]; clinically significant language deficit ascertained by an experienced pediatric neurologist; a difference in PIQ and verbal IQ of at least one standard deviation (15 points) on the WPPSI or WISC-III; monolingual; no hearing impairment; no gross motor deficit, uncontrollable seizures, or other neurologic or muscular disease; no diagnosis of an autism spectrum disorder; and not from an extremely deprived environment.

SPECT procedure

SPECT was performed with the approval of the departmental ethics committee and with informed parental consent. rCBF SPECT scans were performed using a high-resolution, dual-detector SPECT system (ADAC, Vertex, Milpitas, CA, USA) in the department of Nuclear Medicine, Kaohsiung Medical University Hospital. Subjects received an intravenous injection of technetium-99m-D, L-hexamethyl-propylene amine oxime (^{99m}Tc-HMPAO; average 10 Mbq/kg) followed by 5 mg/kg thiamylal sodium about 10 to 30 minutes later. Barbiturate sedation in children has no significant effect on 133-X SPECT [11]. The head was placed in an axial position parallel to the orbitomental line and scanned supine for approximately 15 minutes (128 projections, 64 x 64 matrix acquisition) using high-resolution collimators.

Tomographic slices were reconstructed in the transaxial and coronal planes using a Hanning prefilter with a cutoff frequency of 0.8 cycles/cm, a Ramp filter, and attenuation correction. We used a semiquantitative approach (count rate estimate in selected regions) to obtain an estimate of percentage asymmetry of perfusion between homologous cortical areas. Using 4 x 4 pixel regions of interest (ROI) corresponding to volumes of 1.6 x 1.6 x 0.4 cm^3, ^{99m}Tc-HMPAO uptake levels were calculated for the right and left frontal, medial temporal, lateral temporal, posterior temporal, and occipital lobes, and the cerebellum (above through transaxial cut), and for the right and left lateral temporal and mesial temporal lobes (above through coronal cut). SPECT images were compared with a standard magnetic resonance imaging (MRI) brain atlas [12] to select slices for ROI analysis. The first and second transaxial sections were chosen to identify the cerebellar region and the mesial temporal region separately. The other transaxial section crossed the thalami. The coronal section was chosen to identify the mesial temporal region. The ROI value for each region was the mean of nine independent samples on three separate slices. The relative rCBF values were determined as the regional values divided by the cerebellum value. A left-right index of difference (in percentile) was calculated for each region using the following formula: 2(left rCBF – right rCBF)/(left rCBF + right rCBF).

Results

Eleven boys with the diagnosis of DLD participated in the study. There were no girls because most DLD children seen in our clinic were male. The mean age was 5 years 10 months (range, 4 yr 2 mo to 10 yr 9 mo), mean nonverbal IQ was 107 (range, 82–137) and there were no higher-order subtypes (Table 1). It was not possible to compare patients with age-matched normal children because of the ethical constraints on performing SPECT in normal children, so data were analyzed by comparing the child's bilateral corresponding cerebral regions. Gordon has defined right-left 10% difference as the index of bilateral CBF discrep-

ancy [7], and we applied this principle in our analysis. Ten of the 11 children (90.9%) had significant bilateral flow discrepancy (Table 2). Temporal lobes were involved in all 10 children: the medial-temporal region (transaxial cut) in four, the lateral temporal region (transaxial cut) in five, and the mesial-temporal region (coronal cut) in four. Seven children (Subjects 1–4, 8, 10, 11) had left CBF dominance and three children (Subjects 5–7) had right CBF dominance. There was no difference in IQ, age, hand dominance, or other parameters between children with these two patterns of flow difference. The normal pediatric CBF pattern is left dominance with a right-left difference of less than 10% [13]. In our study, only one child (Subject 9) with DLD demonstrated this pattern.

Discussion

Brain morphology studies using CT/MRI to explore structural abnormalities in children with DLD have mostly revealed normal findings. There is usually no evidence of damage or loss of tissue in visual examination of such scans. In MRI morphometric measurement of the volume of cerebral structures, asymmetry of posterior intrasylvian cortices (eg, planum temporale, planum parietale) may represent a risk factor in children with concomitant language and reading disorders [14–16]. Right perisylvian regions are larger in some children with DLD [17], and left regions are larger than, equal to, or smaller than control volumes [18]. In summary, currently available data do not support a role for abnormal posterior intrasylvian ontogenesis in children with DLD [19].

SPECT is useful to make inferences on DLD pathophysiology. The rationale of using SPECT in evaluating childhood disorders is the presumption that flow and function are related, and that increased perfusion reflects increased neural activity. Development of cognitive function in children is related to increases in rCBF in the corresponding cortical regions, and the time needed to reach relative normal adult rCBFs may be considered as an index of regional maturation. Global CBF increases after infancy to a peak at around 5 to 6 years of age then gradually decreases, approaching adult values in the late teens; different regions show somewhat different patterns [11, 20–23]. Denays et al pioneered in using SPECT in children with developmental dysphasia through visual inspection of scans [24]. They reported hypoperfusion of the left inferior frontal region in children with a purely expressive subtype and hypoperfusion of the left temporoparietal and superior frontal regions in children with mixed receptive-expressive subtype. Our study applied a different analytic approach, using semi-quantitative analysis. By defining bilateral asymmetry to be an rCBF difference of at least 10%, 90.9% of our subjects had meaningful left-right brain functional asymmetry, especially in temporal lobes.

Our study used overly broad phenotypes and included heterogeneous DLD subjects. Current diagnostic methods for DLD inevitably created problems

Table 1. Clinical characteristics

Subject	Sex	Age at SPECT	VIQ/PIQ*	Leiter IQ	Handedness	DLD subtype
1	M	7 yr 6 mo	70/86	105	L	Mixed
2	M	5 yr 9 mo	55/97	NA	R	Mixed
3	M	5 yr 3 mo	78/116	92	R	Mixed
4	M	4 yr 5 mo	80/109	NA	R	Expressive
5	M	6 yr 1 mo	73/113	NA	R	Expressive
6	M	5 yr 4 mo	53/82	82	R	Mixed
7	M	4 yr 10 mo	x/106	137	R	Mixed
8	M	10 yr 9 mo	65/107	NA	R	Expressive
9	M	4 yr 2 mo	62/97	101	R	Expressive
10	M	4 yr 2 mo	79/115	132	R	Mixed
11	M	6 yr	63/102	109	R	Mixed

*VIQ/PIQ by WPPSI or WISC-III. SPECT = single photon emission computerized tomography; VIQ = verbal intelligence quotient; PIQ = performance intelligence quotient; IQ = intelligence quotient; DLD = developmental language disorder; M = male; L = left; R = right; NA = not available.

in identification validity and subject heterogeneity. We recruited subjects based not on a child's performance in a standardized language test, but on clinician's judgment together with discrepancy in subscale scores obtained from standardized cognitive tests. We did not apply standardized language tests because they are not available in Mandarin for Taiwan. However, this is not a major drawback because some researchers recommend that DLD diagnosis should rest on the judgment of the clinician assessing the child who exhibits the problem, rather than on formal language tests [1].

Another source of heterogeneity in DLD studies comes from developmental change. The clinical picture of DLD can change markedly with age. Many young children presenting with DLD in the preschool years appear to grow out of their difficulties during follow-up [25]. Thus, if older DLD subjects are recruited, their problems will be more severe with persistent phenotypes. In our study, mean age was 5 years 10 months, with eight children less than 6 years old. Our subjects were much younger than those in previous studies which recruited school-age children, so our results may reflect the function of a much younger and more immature brain. However, due to the small sample size, the results of this study should be considered preliminary. If confirmed in future large-scale research, this found dysfunction could have important theoretical implications.

Longitudinal follow-up studies of children with DLD have demonstrated that most of these children can speak adequately by school age, but many will have difficulty in learning to read and write [26–28]. The unpredictable outcome and diverse opinions regarding intervention demand more studies in this field. Linking functional deficits to specific neurodevelopmental events should be the focus of future research, so that more effective interventions can be designed. Also, longitudinal follow-up of brain imaging studies is necessary to determine whether observed individual difference is cause or consequence, and whether normal central nervous system maturation or rehabilitation programs affect the unfolding of DLD in its varying stages of development.

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Table 2. Regional cerebral blood flow (rCBF) and left-right index (%)

Subject	Frontal			Occipital			Temporal			Post-temporal			Medial-temporal			Lat-temporal			Lat-temporal†			Mes-temporal†		
	rCBF			rCBF			rCBF			rCBF			rCBF			rCBF			rCBF			rCBF		
	R	L	Index* (%)	R	L	Index* (%)	R	L	Index* (%)	R	L	Index* (%)	R	L	Index* (%)	R	L	Index* (%)	R	L	Index* (%)	R	L	Index* (%)
1	88.6	85.4	-3.7	105.8	111.3	5.1	100.5	96.9	-3.6	102.9	102.3	-0.6	84.3	95.0	**11.9**	88.9	91.8	3.2	98.0	101.6	3.6	91.0	90.3	-0.8
2	102.4	106.1	3.5	95.9	105.9	9.9	106.8	129.5	**19.2**	110.9	126.0	**12.7**	77.9	95.6	**20.4**	94.7	92.8	-2.0	103.5	106.0	2.4	93.8	92.8	-1.1
3	94.9	100.5	5.7	99.4	99.3	-0.1	92.7	101.4	9.0	100.9	114.2	**12.4**	87.9	92.5	5.1	94.2	115.4	**20.2**	101.3	110.6	8.8	84.0	92.7	9.8
4	110.9	121.3	9.0	107.3	126.3	**16.3**	118.4	127.3	7.2	118.4	142.0	**18.1**	101.3	110.7	8.9	80.0	132.8	**49.6**	105.6	146.8	**32.6**	95.9	98.0	2.2
5	93.8	99.0	5.4	94.0	96.4	2.5	102.5	103.8	1.3	104.6	107.2	2.5	85.1	81.7	-4.1	101.3	86.9	**-15.3**	96.1	87.7	9.1	81.0	88.6	9.0
6	102.8	99.4	-3.4	106.3	104.2	-2.0	113.5	108.4	-4.6	107.4	110.9	3.2	103.0	90.7	**-12.7**	103.9	87.1	**-17.6**	106.5	100.6	-5.7	95.5	86.5	-9.9
7	118.0	107.8	-9.0	104.8	110.2	5.0	116.3	118.7	2.0	120.5	114.1	-5.5	101.2	92.3	-9.2	98.5	97.8	-0.7	118.1	105.0	**-11.7**	95.0	81.5	**-15.3**
8	89.3	97.8	9.1	94.6	91.3	-3.6	96.2	108.8	**12.3**	100.2	106.5	6.1	74.5	90.9	**19.8**	73.1	101.0	**32.1**	80.6	86.1	6.6	71.8	94.3	**27.1**
9	90.6	97.1	6.9	96.5	97.1	0.6	97.5	103.3	5.8	104.8	105.2	0.4	86.9	83.7	-3.8	94.2	96.2	2.1	95.9	95.3	0.6	82.3	88.1	6.8
10	95.3	98.9	3.7	98.5	92.3	-6.5	108.6	110.0	1.3	108.0	111.3	3.0	94.4	103.7	9.4	91.0	85.2	-6.6	90.1	92.7	2.8	78.2	95.8	**20.2**
11	86.0	96.0	**11.0**	94.9	93.9	-1.1	98.8	102.3	3.5	100.9	111.1	9.6	73.0	73.7	1.0	87.1	92.4	5.9	90.9	88.4	-2.8	71.9	80.2	**10.9**

Figures in bold indicate difference more than 10%. *Index = 2(L-R)/(L+R) x 100%. †Calculation on coronal reconstruction. Post = posterior; Lat = lateral; Mes = mesial.

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發展性語言疾患孩童之 ^{99m}Tc-HMPAO 腦質灌注攝影發現

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臨床上對於語言發展遲緩的孩童，若其感官系統正常，無智能障礙，也不屬於自閉症候群時，則診斷為發展性語言疾患。本研究係以 ^{99m}Tc-HMPAO 腦質灌注攝影評估 11 位有“發展性語言疾患”的孩童（平均年齡 5 歲 10 個月，範圍 4 歲 2 個月－10 歲 9 個月）；平均非語文智力測驗得智商 107，範圍 82－137）的大腦血流分布狀況。結果顯示，若將左右兩側對稱區域大腦血流量差異超過 10% 定義為“顯著差異”時，10 位孩童（90.9%）左右大腦的血流分布有顯著差異，所有的小孩均為顳葉有問題（5/11 在顳葉外側，4/11 在顳葉內側，4/11 在顳葉中部）。本研究係少量個案之初期研究，結果顯示，發展性語言疾患可能是大腦語言相關部位產生潛在的神經生物問題所致。

關鍵詞：發展性語言疾患；單光子電腦斷層掃描

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