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www.jkns.or.kr 10.3340/jkns.2008.44.4.240
Print ISSN 2005-3711 On-line ISSN 1598-7876
J Korean Neurosurg Soc 44 : 240-244, 2008
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Clinical Article

The First Neurosurgical Analysis of 8 Korean Children with Sotos Syndrome

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Objective : Sotos Syndrome is characterized by macrocephaly, overgrowth, and developmental delay, and more than 300 patients have been reported worldwide to date. The authors reviewed the clinical characteristics of 8 patients with Sotos Syndrome in Korea for a new understanding and treatment strategies.
Methods : The medical records of a total of eight Korean children with Sotos Syndrome were reviewed. All patients underwent developmental checkup, lumbar punctures for measurement of intracranial pressure (ICP), brain and spine magnetic resonance imaging and computerized tomography.
Results : All 8 patients showed macrocephaly and the characteristic craniofacial features of Sotos Syndrome. Other clinical characteristics shown were overgrowth (7/8), developmental delay (7/8), congenital heart defect (3/8), flat foot (8/8), scoliosis (4/8), spina bifida (8/8), hydrocephalus (4/8), cavum vergae (3/8), and increased subdural fluid collection (5/8). Mean ICP measured via lumbar puncture was 27.35 ± 6.25 cm H_2O (range 20 to 36 cm H_2O). Two patients received ventriculo-peritoneal shunt, and 1 patient underwent subduro-peritoneal shunt with improvement. Spinal orthosis was applied to 4/5 patients with scoliosis and 4/8 children with flat foot were provided with foot orthosis.
Conclusion : In this first Korean study of 8 Sotos Syndrome patients we demonstrated the presence of spina bifida and increased ICP, which had not been previously described. The authors therefore suggest that all patients with Sotos Syndrome should undergo examination for the presence of spina bifida, and that shunt procedures would improve development and alleviate clinical symptoms.

KEY WORDS : Sotos Syndrome · Spina bifida · Intracranial pressure · Hydrocephalus · Shunt.

INTRODUCTION

Sotos Sydrome was first described in 1964 by Sotos[18], and occurs in approximately 1/10,000-1/50,000 of the birth, and the prevalence is estimated to be between 1/10,000-1/50,000[17]. Cole and Hughes[6] described the clinical characteristics of this syndrome, and it consists of macrocrania, general overgrowth, long cranium, narrow face, and mental retardation, and accompanying neuroradiologic manifestations are hydrocephalus, subdural fluid collection, midline abnormalities such as the cavum septum pellucidum, kyphoscoliosis, and cardiac defects[4,7,8,16]. Developmental delay and seizures, and attention deficit may also present[5,6,15]. Clinical criteria include facial gestalt, macrocephaly, advanced growth, and the presence of developmental delay[6,19]. Diagnostic criteria have changed from morphologic abnormality to genetic abnormality after 2002[11]. More than 300 patients have been reported worldwide, and 5 in Korea as individual case reports[1,9,10,14]. However, all reports were pointed only to morphological abnormalities, not to increased intracranial pressure, importance of shunt procedure, and accompanied spina bifida. The authors reviewed the clinical characteristics of 8 patients with Sotos Syndrome in Korea including increased intracranial pressure, importance of ventriculo-peritoneal or subduro-peritoneal shunt, and accompanied spina bifida, and suggest a new understanding and treatment strategies for such patients.

MATERIALS AND METHODS

Age, gender, and neurological symptoms were assesses by reviewing the medical records of the 8 patients who were recruited from the association of Sotos Syndrome. Only

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one patient was enrolled in this study from 5 patients of previous Korean case reports because 4 patients were lost. Six were male children and 2 were female. The age ranged from 1-9.4 years, and the mean age was 4.6 years. Gestational age at the time of delivery ranged from 35-41 weeks, and the mean gestational age was 38.6±4.2 weeks. The ages of fathers ranged from 28-36 years, and the mean was 32.6±5.6 years. The mothers' ages ranged 25-33 years with a mean of 29.7±5.5 years (Table 1).

All patients underwent ICP measurement by lumbar puncture under general anesthesia. Neuro-radiological status was evaluated by magnetic resonance imaging (MRI) and computerized tomography (CT).

The age-adjusted head circumference of greater than 97 percentile with Nelhaus head circumference curve was defined as macrocephaly. Similarly, overgrowth was defined as greater than 97 percentile height for age-adjusted head. Craniofacial phenotype was evaluated by iconography of the patient to assess the disproportionate prominence of the forehead, macro-dolichocephaly, downslanting palpebral fissures, and flat nasal bridge (Fig 1).

Developmental delay was defined as delay in 2 or more of the developmental domains (gross, fine motor, speech, language, cognition, social and personal activities of daily living)[19].

Subdural fluid collection was diagnosed when subdural space was observed to be increased to more than 5 mm in the supra-tentorial or posterior fossa space[3] (Fig 2). Chiari malformation was defined as downward displacement of the cerebellum from the foramen magnum to more than 5 mm by MRI imaging. Hydrocephalus was deemed to be present when the Evan's ratio was greater than 0.3 by CT imaging.

RESULTS

All patients displayed macrocephaly. Also, all showed the typical craniofacial features of Sotos Syndrome, i.e., prominent forehead, downslanting palpebral fissures, and flat nasal bridge. Seven of eight patients were of greater than 97 percentile in height. Seven of eight patients showed delay in speech and performance skill, while all patients displayed delayed cognition, and social/personal activities. Congenital heart defect (CHD) was observed in 3 of 8 patients. Flat foot was seen in all patients, while scoliosis was present in 5, and chiari malformation in only

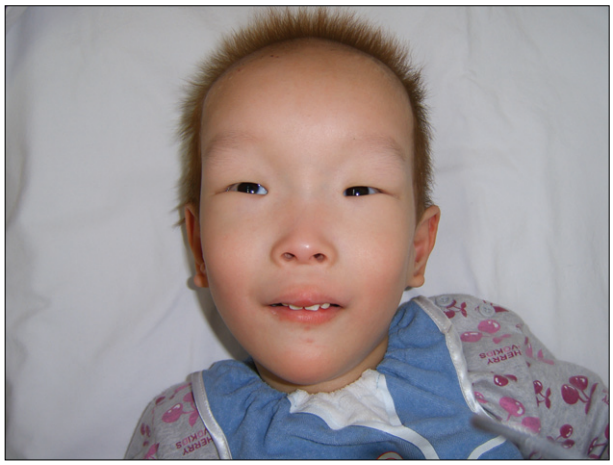

Fig. 1. Characteristic face photograph of the patient showing a large head with long anteroposterior length, low nose, wide intercanthal width and frontal bossing.

Table 1. Demographic data of 8 patients

Variable	Patient number							
	1	2	3	4	5	6	7	8
Sex	F	M	M	F	M	M	M	M
Age (years)	1	2.3	2.4	4.10	5.3	5.3	7.10	9.4
Gestational age (weeks)	40	41	36	40	35	37	39	41
Parent age (years)								
Father	36	35	35	33	31	31	32	28
Mother	29	31	32	30	31	33	25	27

Table 2. Clinical manifestation and neuroradiologic findings of 8 Sotos Syndrome patients

Characteristic	Patient number								Total number of cases / all patients
	1	2	3	4	5	6	7	8	
Macrocephaly	+	+	+	+	+	+	+	+	8 / 8
Prominent forehead	+	+	+	+	+	+	+	+	8 / 8
Downslanting palpebral fissure	+	+	+	+	+	+	+	+	8 / 8
Flat nasal bridge	+	+	+	+	+	+	+	+	8 / 8
Overgrowth	+	+	+	+	+	+	+	−	7 / 8
Developmental delay	+	+	+	+	+	+	+	+	8 / 8
Cardiac anomaly	−	VSD	−	ASD	−	−	−	PDA	3 / 8
Flat foot	+	+	+	+	+	+	+	+	8 / 8
Subdural fluid collection	+	+	+	−	+	+	−	−	5 / 8
Chiari malformation	−	−	−	−	−	−	−	+	1 / 8
Scoliosis	+	+	+	−	+	+	−	−	5 / 8
Spina bifida	+	+	+	+	+	+	+	+	8 / 8
Hydrocephalus	+	−	−	−	+	+	+	−	4 / 8
ICP (cmH20)	28	26.8	26.5	23	36	35	23.5	20	Mean ICP=27.35

VSD : ventral septal defect, ASD : atrial septal defect, PDA : patent ductus arteriosus, ICP : intracerebral pressure

1 patient.

All patients were with spina bifida of the lumbosacral region (Fig 3). Six of the 8 were located at the 4th, 5th lumbar vertebrae and sacrum, and 2 were situated at the 5th lumbar vertebrae and sacrum. Other anomalies such as thickening of the film terminale or tethered cords were not observed.

The mean ICP as measured by lumbar puncture was 27.35 ± 6.25 cmH_2O (range 20 to 36 cmH_2O). Hydrocephalus was present in 4 of 8 patients, among whom the Evan's ratio was greater than 0.4, and 2 were between 0.3 and 0.4 (Table 2). In 2 patients with hydrocephalus, the trigone was prominent, and 1 patient had a prominent occipital horn was in 1 patient. One patient had both prominent trigone and occipital horn.

There were thinning of the corpus callosum, cavum septum pellucidum, cavum vergae, cavum velum interpositum, periventricular leukomalacia, and subdural fluid collection (Table 3).

Treatments consisted of ventriculo-peritoneal shunting in the 2 patients with greater than 0.4 Evan's ratio, subduro-peritoneal shunting in 1 patient with subdural fluid collection and an Evan's ratio between 0.3 and 0.4, but the remaining patient did not undergo shunting. All three patients with shunting procedures were improved in symptoms and signs including disappearance of syringomyelia, enhanced attention, and improved learning. Among the 4 of 5 patients with scoliosis spinal orthosis was applied, and foot orthosis was administered for the 4 of 8 with flat foot (Table 4).

Table 3. Neuroimaging findings of 8 Sotos Syndrome patients

Neuromaging findings	Patient number								Total number of cases/ all patients
	1	2	3	4	5	6	7	8	
Ventricles									
Large	+	−	−	−	+	+	+	−	4/8
Prominent trigone	+	−	−	−	+	−	+	−	3/8
Prominent occipital horn	−	+	−	−	−	+	−	−	2/8
Extracerebral fluid									
Supratentorial	+	+	+	−	+	+	−	−	4/8
Posterior fossa	−	+	−	−	−	−	−	−	1/8
Midline anomalies									
Cavum septum Pellucidum	−	−	−	+	−	−	−	−	1/8
Cavum vergae	+	+	−	−	−	+	−	−	3/8
Cavum velum interpositum	−	−	−	−	+	−	−	−	1/8
Macrocisterna Magna	−	−	−	−	−	−	−	−	0/8
Agenesis of CC	−	−	−	−	−	−	−	−	0/8
Hypoplasia of CC	−	−	−	−	−	−	−	−	0/8
Thinning of CC body	−	+	−	−	+	+	−	−	3/8
Migrational									
Heterotopias	−	−	−	−	−	−	−	−	0/8
Others									
PVL	+	−	−	−	−	−	−	−	1/8
Macrocerebellum	−	−	−	−	−	−	−	−	0/8
Open operculum	−	−	−	−	−	−	−	−	0/8

CC : corpus callosum, PVL : periventricular leukomalacia

Table 4. Treatment of 8 Sotos Syndrome patients

Treatment	Patient number								Total number of cases / all patients
	1	2	3	4	5	6	7	8	
Shunt	VP	−	−	−	SP	VP	−	−	3 / 8
Spinal orthosis	−	+	+	−	+	+	−	−	4 / 8
Foot orthosis	−	+	+	+	+	−	−	−	4 / 8

VP : ventriculo−peritoneal shunt, SP : subduro−peritoneal shunt

DISCUSSION

General clinical manifestations that are apparent at birth are increased head, height, and weight for gestational age, dolichocephalic macrocrania, frontal bossing, prominent forehead, and ocular hypertelorism. Facial characteristics are downslanting palpebral fissure and flat nasal bride, high arched palate, and pointed chin[2,6,13]. Other accompanying abnormalities that have been observed are CHD, flat foot, scoliosis, and genitourinary anomalies[6-8,13,20,22].

The clinical criteria for diagnosis of Sotos Syndrome are the presence of facial gestalt, macrocephaly, advanced growth, and the presence of developmental delay[6,19]. Kurotaki et al.[11] reported that the genetic mechanism of Sotos Syndrome was due to abnormality of the NSD1 (nuclear receptor binding SET-domain-containing gene genetic abnormality). In support of this observation, Tatton-Brown et al.[22] studied the clinical features of 239 patients with Sotos Syndrome and showed that NSD1 abnormality was found in more than 90% of the patients, and concluded that the diagnosis of Sotos Syndrome should focus on assessing genetic abnormalities rather than morphologic abnormalities.

Treatment for patients with Sotos Syndrome consists of therapy for jaundice in the neonatal period, therapy for sucking and swallowing diffic-

ulties, speech therapy for infants, adaptive physical therapy or therapy for cardiac, renal, orthopedic symptoms, followed by treatment for learning, social interaction, and family functioning, with regular follow-up.

The mean gestational age of the patients at birth in this study (38.6 weeks) is similar to that of Cole and Hughes[6] who reported 39 weeks for Sotos Syndrome patients. We observed 7/8 patients with greater than age-adjusted 97 percentile height during childhood, and this figure is also similar to the 37/39 reported by the above authors.

In terms of developmental delay, Srour et al.[19] observed in 3/3 patients with Sotos Syndrome. In the present study, we investigated developmental delay with regard to gross, speech, language, cognition, social and personal activities of daily living, and as we found that all 8 patients showed delay in 2 or more domains, we were able to conclude that all patients were accompanied by developmental delay.

CHD, such as atrial septal defect (ASD), patent ductus arteriosus (PDA) and ventral septal defect (VSD), has been reported to be found in 5/10 Sotos Syndrome patients in a report by Kaneko et al.[8]. Three of the patients in this study had ASD, PDA, or VSD. Therefore, cardiac evaluation with an echocardiogram is suggested to be essential in all patients with Sotos Syndrome.

In the aforementioned study by Cole and Hughes[6] 18/39 Sotos Syndrome patients were found to be with flat foot, while 7/8 were found in our review, among whom 5 underwent orthosis treatment.

Takei et al.[21] and Motohashi et al.[12] reported the presence of dentofacial growth abnormality in 2 and 4 patients, respectively, with Sotos Syndrome, suggesting that dentofacial growth abnormality is a major component of Sotos Syndrome. We were also able to observe this dentofacial abnormality in 3 of 8 of our cases, among whom 1 patient received mandible reconstruction surgery.

According to a series by Schaefer et al.[16], large ventricles, increased extracerebral fluid, and midline anomalies are frequently found in patients with Sotos Syndrome, which was similar to our findings. Hydrocephalus was found in 25 of 40 patients according a study by Schaefer et al., while this was observed to be present in 4 of 8 patients in our study. Among the above patients increased trigone size was detected in 3 of 8 patients, and enlarged occipital horn in 1 patient, demonstrating a marked discrepancy from the 36/40 and 30/40 as reported by Schaefer et al. This discrepancy was similar with respect to increased subdural fluid collection in our study (3/8, and 1/8, respectively) compared to the results of Schaefer et al. 28/40 and 28/40, respectively). The incidence of midline abnormalities were similar to the above authors (3/8 vs. 15/40 cavum vergae), but was significantly dissimilar for cavum septum pellucidum and cavum velum interpositum (1/8 each in our study) compared to Schaefer et al. 16/40 and 7/40, respectively). Other abnormalities such as macrocisterna magna, and agenesis of corpus callosum were not found in our study.

Two recent reports by Haga et al.[7] and Sweeney et al.[20] have described the presence of spinal scoliosis in 5 and 2 patients, respectively, in patients with Sotos Syndrome. We

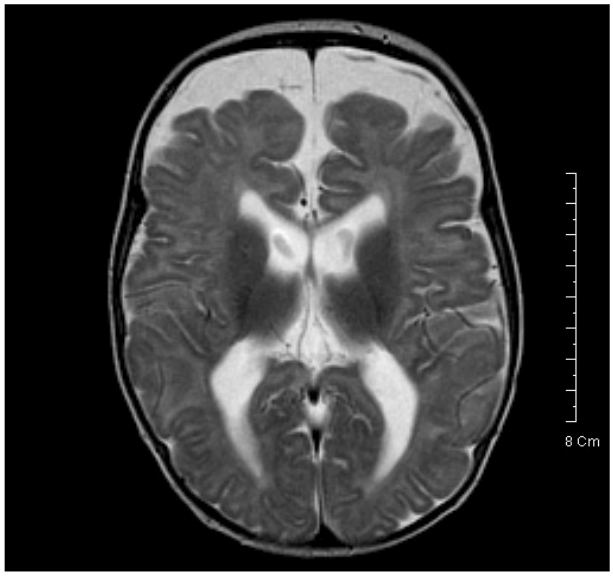

Fig. 2. Magnetic resonance image showing subdural hygroma in the bifrontal area.

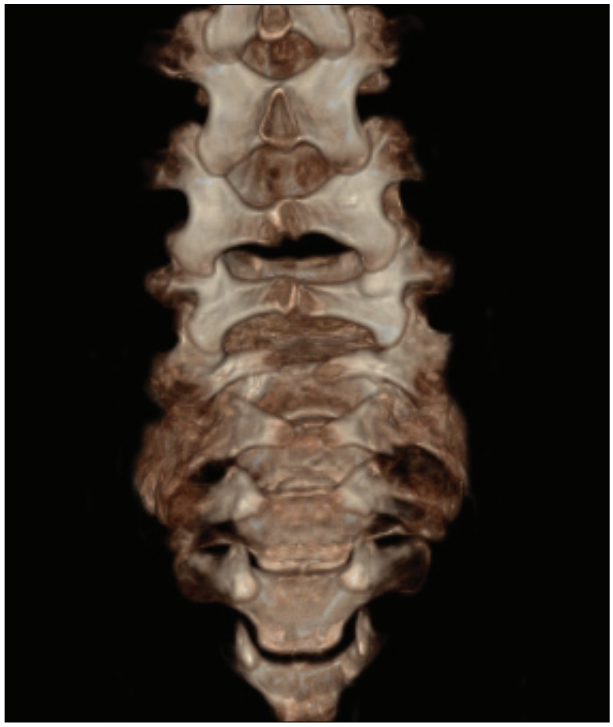

Fig. 3. Computed tomography demons-trating spina bifida in the lumbosacral area.

also observed 5/8 with scoliosis in our study, among whom 4 are receiving orthosis therapy. Search of the past literature has failed to reveal the presence of spina bifida as an accompanying condition in patients with Sotos Syndrome. However, we observed that spina bifida was present in all of our 8 patients by spinal CT scan, that was absolutely higher incidence than that of normal population. Although none of our 8 patients were found with anomalies such as thickened film terminale, tethered cord, or dermal sinus tract, that requires surgical correction, the high incidence of spina bifida in our patients necessitates clinical evaluation of all Sotos Syndrome patients for the presence of spina bifida.

While patients with Sotos Syndrome also commonly demonstrate hydrocephalus, ventricular dilation, and subdural fluid collection, no previous studies have examined intracranial pressure in these patients. We observed, however, that all 8 of our Sotos Syndrome patients had high intracranial pressure, the mean level being 27.35 cmH_2O. In light of results previously published by the same authors of this study[14], which showed that shunt procedures for Sotos Syndrome patients alleviated clinical symptoms, we suggest that early shunting would decrease intracranial pressure, prevent ventricular dilation and subdural fluid collection, which would ultimately improve developmental delay and associated clinical symptoms. As demonstrated in 2 of our patients with markedly high intracranial pressure, seizures, irritability, and eye contact inability, the shunt procedure was able to produce significant improvement.

CONCLUSION

We confirmed for the first time in a study of 8 Korean patients with Sotos Syndrome that spina bifida and increased intracranial pressure are associated conditions. The authors of this study therefore suggest that all patients with Sotos Syndrome should undergo examination for the presence of spina bifida, and that shunt procedures would improve development and alleviate clinical symptoms.

References

1. Ahn HJ, Kim YT, Seol IH, Shin JH : Two Cases of Cerebral Gigantism (Sotos Syndrome). **J Korean Pediatr Soc 33** : 1153-1156, 1990
2. Allanson JE, Cole TR : Sotos Syndrome : evolution of facial phenotype subjective and objective assessment. **Am J Med Genet 65** : 13-20, 1996
3. Aoki N : Chronic subdural hematoma in infancy. Clinical analysis of 30 cases in the CT era. **J Neurosurg 73** : 201-205, 1990
4. Aoki N, Oikawa A, Sakai T : Serial neuroimaging studies in Sotos Syndrome (cerebral gigantism Syndrome). **Neurol Res 20** : 149-152, 1998
5. Cohen MM Jr : Mental deficiency, alterations in performance, and CNS abnormalities in overgrowth Syndromes. **Am J Med Genet C Semin Med Genet 117C** : 49-56, 2003
6. Cole TR, Hughes HE: Sotos Syndrome : a study of the diagnostic criteria and natural history. **J Med Genet 31** : 20-32, 1994
7. Haga N, Nakamura S, Shimode M, Yanagisako Y, Iwaya T : Scoliosis in cerebral gigantism, Sotos Syndrome. A case report. **Spine 21** : 1699-1702, 1996
8. Kaneko H, Tsukahara M, Tachibana H, Kurashige H, Kuwano A, Kajii T : Congenital heart defects in Sotos sequence. **Am J Med Genet 26** : 569-576, 1987
9. Kim IS, Kim JH, Choi YY, Ma JS, Hwang TJ : A Case of Sotos Syndrome. **J Korean Pediatr Soc 38** : 725-729, 1995
10. Kim SB, Yang S, Kim HD, Oh PS, Cha JK, Shin JH : A Case of Cerebral Gigantism (Sotos Syndrome). **J Korean Soc Pediatr Endocrinol 7** : 122-127, 2002
11. Kurotaki N, Imaizumi K, Harada N, Masuno M, Kondoh T, Nagai T, et al : Haploinsufficiency of NSD1 causes Sotos Syndrome. **Nat Genet 30** : 365-366, 2002
12. Motohashi N, Pruzansky S, Kawata T : Roentgencephalometric analysis of cerebral gigantism : report of four patients. **J Craniofac Genet Dev Biol 1** : 73-94, 1981
13. Opitz JM, Weaver DW, Reynolds JF Jr : The Syndromes of Sotos and Weaver : reports and review. **Am J Med Genet 79** : 294-304, 1998
14. Park SW, Park MS, Hwang JS, Shin YS, Yoon SH : A case of Sotos Syndrome with subduroperitoneal shunt. **Pediatr Neurosurg 42** : 174-179, 2006
15. Sarimski K : Behavioural and emotional characteristics in children with Sotos Syndrome and learning disabilities. **Dev Med Child Neurol 45** : 172-178, 2003
16. Schaefer GB, Bodensteiner JB, Buehler BA, Lin A, Cole TR : The neuroimaging findings in Sotos Syndrome. **Am J Med Genet 68** : 462-465, 1997
17. Sotos JF, Overgrowth, Section V : Syndromes and other disorders associated with overgrowth. **Clin Pediatr (Phila) 36** : 89-103, 1997
18. Sotos JF, Dodge PR, Muirhead DD, Crawford JD, Talbot NB : Cerebral gigantism in childhood. A Syndrome of excessively rapid growth and acromegalic features and a nonprogressive neurologic disorder. **N Engl J Med 271** : 109-116, 1964
19. Srour M, Mazer B, Shevell M : Diagnosing Sotos Syndrome in the setting of global developmental delay and macrocephaly. **J Child Neurol 21** : 287-290, 2006
20. Sweeney E, Fryer A, Donnai D : Sotos Syndrome: two cases with severe scoliosis. **Clin Dysmorphol 11** : 121-124, 2002
21. Takei K, Sueishi K, Yamaguchi H, Ohtawa Y : Dentofacial growth in patients with Sotos syndrome. **Bull Tokyo Dent Coll 48** : 73-85, 2007
22. Tatton-Brown K, Douglas J, Coleman K, Baujat G, Cole TR, Das S, et al : Genotype-phenotype associations in Sotos Syndrome: an analysis of 266 individuals with NSD1 aberrations. **Am J Hum Genet 77** : 193-204, 2005