소아 길랑-바레 증후군 진단에서 척추 MRI로의 패러다임 변화

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Paradigm Shift to Spinal Magnetic Resonance Imaging the Diagnosis of Guillain-Barré Syndrome in Children

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Purpose: This study was aimed to evaluate the clinical value of gadolinium-enhanced spinal magnetic resonance imaging (MRI) in the diagnosis of Guillain-Barré syndrome (GBS) by comparing it with cerebrospinal fluid (CSF) and nerve conduction studies (NCS) in children.

Method: A single center, retrospective analysis of clinical investigations undertaken in children with GBS over a 5-year period was performed. The patients' respective medical records, including spinal MRIs and nerve conduction studies, were reviewed.

Results: A total of seventeen children (mean age 5.3 ± 3.6 years; males, 12, females, 5) were enrolled in the study. Twelve out of 17 children (71%) showed gadolinium nerve root enhancement, mostly anterior along with posterior roots (10/12, 83%) at 4.1 days of illness, compared to CSF (2/11, 11%) at 2.5 days and NCS (11/17, 64%) at 7.4 days of illness ($P < 0.05$). In addition, it appeared the more severe symptoms showed more positive findings; however, the difference was statistically insignificant ($P > 0.05$).

Conclusion: In conclusion, NCS are a standard diagnostic tool for GBS. This study supports the gadolinium-enhanced spinal MRI as a valuable investigating technique in the early diagnosis of GBS, although it is not necessarily superior. However, further studies are needed to elucidate the mechanisms and to strengthen the results.

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Key Words: Guillain-Barré syndrome, magnetic resonance imaging, diagnosis, child

Introduction

Guillain-Barré syndrome (GBS) is an acute inflammatory demyelinating polyneuropathy (AIDP) that typically presents as an ascending flaccid paralysis following an antecedent infection. It is one of the most common causes of acute flaccid paralysis in children worldwide¹⁻³. Currently, the diagnosis is made by clinical features supported by nerve conduction studies (NCS) and cerebrospinal fluid (CSF) analysis, which may be normal during the first 1–2 weeks of illness^{1,4-7}. However, with easier access to MRI, the advantages of gadolinium-enhanced spinal MRI in children with suspected GBS have been stressed⁸⁻¹⁰. The spinal MRI can allow physicians to make additional diagnoses of potentially catastrophic conditions, such as spinal cord compression and transverse myelitis,

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diagnoses that are not possible with NCS and CSF analysis alone.

We, therefore, aimed to evaluate the usefulness of early diagnosis of the gadolinium-enhanced spinal MRI in children with suspected GBS, and to compare it with the traditionally standard diagnostic tools of CSF analysis and NCS.

Materials and Methods

Children under the age of 19 years diagnosed with GBS at Kyungpook National University Hospital, Daegu, Korea from June 2009 to June 2014 were identified as potential study candidates. A total of 17 children (mean age 5.3 years; range, 8 months–14 years) were included and their clinical data were retrospectively reviewed. The duration of clinical symptoms was calculated from the first day motor symptoms were noted. Motor symptoms were graded on a six-point scale proposed by Hughes¹¹⁾. A lumbar puncture (LP) was done before the immunoglobulin treatment and CSF albumin–cytological dissociation was considered to be present if there was elevated total protein in the absence of significant pleocytosis (<50 mononuclear cells/mm³). NCS was performed during the acute phase and considered positive if the results were consistent with a demyelination or axonal polyneuropathy under the Albers and Hadden criteria^{12,13)}. All patients had a contrast-enhanced spinal MRI scans on a 3.0 Tesla (Siemens, Germany). The contrast enhancement pattern was determined by the neuroradiologist. The study was approved by the internal review (KNUH 2015-01-040).

Data analysis was conducted using SPSS, version 20.0 (SPSS, Inc, an IBM Company, Chicago, IL). Continuous variables are described as mean $\pm$ S.D., and qualitative variables are expressed as percentages. Fisher's exact test for binomial proportion was

performed to compare Fisher's exact test and Two-tailed null hypotheses of no difference were rejected if *P* value was less than 0.05.

Results

A total of 17 children with GBS (mean age 5.3 years; range, 8 months–14 years) who presented at our hospital over the past 5 years were included in the study. The preceding illnesses included upper respiratory infections, non-specific febrile illnesses, acute gastroenteritis, and vaccination. The mean period prior to presentation was 10 days (range, 1–21 days). The patients' symptoms were graded on a six-point scale proposed by Hughes; all were barely able to walk at the time of admission (Grade 2: 18%, Grade 3: 35%, and Grade 4: 47%) (Table 1). The subjects underwent a lumbar puncture on the day of presentation at a mean of 3 days from the onset of motor symptoms (range, 1–5 days). Two (11.7%) patients demonstrated albuminocytological dissociation. NCS were performed at a mean of 7 days after the onset of motor symptoms (range, 1–12 days). Eleven (64.7%) of the patients were considered to be positive under the Albers criteria. Four (36%) of the patients showed abnormalities of H reflexes and F responses that are frequently noted in early AIDP. Sensory nerve action potential (SNAP) amplitudes were abnormal in 4 patients (36%). Sensory responses were absent in 2 patients (18%) and of reduced amplitude in 2 patients (18%). In one patient, NCS showed no evidence of demyelination or reduced compound muscle action potential (CMAP) amplitude in two or more nerves. Gadolinium-enhanced spinal MRI scans were performed at a mean 4 days from the onset of motor symptoms (range, 1–9 days). In each case, T1-weighted, T2-weighted and contrast-enhanced images of the entire spine were obtained. Twelve (70.5%) patients' MRIs showed nerve root enhancement. As compared with the CSF

Table 1. Demographic and Clinical Characteristics of the Subjects (n=17)

Age (years)	5.3 $\pm$ 3.6
M:F	12:5
Preceding illnesses	URI (n=10)
	NSFI (n=4)
	AGE (n=2)
	Vaccination (n=1)
Period prior to presentation (days)	10.2 $\pm$ 5.8
Clinical features/severity* 2 (n=3)	
	3 (n=6)
	4 (n=8)

M, male; F, female; URI, upper respiratory illness; NSFI, non-specific febrile illness; AGE, acute gastroenteritis.

*Hughes functional classification.

Table 2. Positivity of the Tests from the Subjects (n=17)

	CSF	NCV	MRI	
Positive	2/17 (11.7%)	11/17 (64.7%)	12/17 (70.5%)	<i>P</i> =0.0038*
				<i>P</i> =0.0013 [†]
				1.0 [‡]
Time to procedure (days)	2.5 $\pm$ 2.3	7.4 $\pm$ 3.7	4.1 $\pm$ 3.2	

CSF, cerebrospinal fluid; NCV, nerve conduction velocity; MRI, magnetic resonance imaging.

*CSF vs NCV, Fisher exact two tailed test.

[†]CSF vs MRI, Fisher exact two tailed test.

[‡]NCV vs MRI, Yates Chi-Square test.

analysis and NCS, contrast-enhanced MRI appeared a better diagnostic tool than CSF analysis ($P=0.0038$, $P=0.0013$) (Table 2). Regardless the severity of motor symptoms, the majority (>80%) of the MRIs revealed an enhancement of the anterior and the posterior nerve roots, which were more prominent anteriorly, even though the difference was not statistically significant (Table 3, Fig. 1). In one patient, post-contrast images demonstrated a diffuse enhancement of aggregated nerve roots of the cauda equina and conus medullaris (Fig. 2). In addition, the positive probability seemed to correlate with the severity of motor symptoms, but the correlation was not statistically significant (Table 4). Not every child had follow-up imaging, but serial MRI revealed complete resolution in one patient.

Discussion

Guillain-Barré syndrome is an acute, immune-mediated, mostly demyelinating polyneuropathy that often follows an antecedent infection or vaccination. The practical diagnosis relies mainly on the clinical findings from the history and examination, although CSF analysis and NCS usually provide a supporting evidence of the diagnosis¹⁴⁾. GBS in children differs from those in adults, not only in the clinical manifestations but also in etiologies. Apart from the mimics and variants of GBS^{7,15-22)}, the correct diagnosis is not easy due to the limited history and challenging examination and procedures. MRI is easily

Table 3. Enhancement of Nerve Roots on Spine MRI and Clinical Severity (n=12)

	Grade 2-3 (n=5)	Grade 4 (n=7)	Fisher exact two-tailed test
Anterior	1/5 (20%)	1/7 (14%)	1.0
Both	4/5 (80%)	6/7 (86%)	1.0

Fig. 1. T₁ weighted postcontrast axial image in a 5 year old boy with Guillain-Barré Syndrome shows a bright enhancement of ventral and dorsal nerve roots of spinal cord.

available worldwide, and the advantage of spinal post-gadolinium MRI has been suggested that it not only supports the clinical diagnosis of GBS, but it excludes important differential diagnoses^{8-10,23,24)}.

A total of 17 children with GBS, mostly in preschool age, were included in the study. The preceding illnesses included upper respiratory infections, non-specific febrile illnesses, acute gastroenteritis, and vaccination. Recent data on the pathology and pathophysiology of GBS emphasized the important role of *Campylobacter jejuni* infection in generating anti-ganglioside antibodies (GM1 in AIDP, GQ1b in MFS and GD1a in AMAN), which damage myelin in AIDP and MFS and axons in AMAN²⁵⁾. We therefore measured serum antiganglioside antibodies using enzyme-linked immunosorbent assay (ELISA). GM1 was identified only in one patient, in the absence of *Campylobacter jejuni* infection.

The mean period prior to presentation was 10 days (range: 1-21 days). Based on a six-point scale proposed by Hughes, they barely walked at the time of admission (Grade 2:18%, Grade 3: 35%, Grade 4:47). With the advance of treatment with intravenous immunoglobulin (IVIG) or plasmapheresis, we rarely see severe or far-progressed cases these days.

GBS typically presents with the albuminocytological dissociation.

Table 4. Positivity of the Tests and Clinical Severity (n=17)

	Grade 2-3 (n=9)	Grade 4 (n=8)	Fisher exact two-tailed test
NCV	5/9 (56%)	6/8 (75%)	0.62
MRI	5/9 (56%)	7/8 (88%)	0.29

NCV, nerve conduction velocity; MRI, magnetic resonance imaging.

Fig. 2. T₁ weighted postcontrast sagittal images demonstrate a diffuse enhancement of aggregated nerve roots of cauda equine as well as conus medullaris.

tion of an increase in CSF protein in the absence of significant pleocytosis, of less than 50 cells/mm³ (26-28). In this study, this was observed in only 11% of the subjects in their first week (1-5 days) of illness, which is far less than the previous reports^{7,28,29}. However, considering the safety, discomfort, and its diagnostic accuracy, we did not perform the follow-up lumbar punctures.

Since NCS are gold standard tool for diagnosis, every patient went through the test. They were performed in 1 to 12 days, mostly in 5-10 days from motor symptom onset. Eleven out of them (64%) were considered positive mainly by Hadden criteria, and this is not bad for a diagnostic yield when compared to a previous study^{6,30,31}. In one patient, we double-checked the data by using Albers criteria, because it was reported as the most sensitive criteria³¹. Four out of them (36%) showed abnormalities of H reflexes and F responses that are often noted in early AIDP³¹. SNAP amplitudes were abnormal in 4 patients (36%), with absent responses in 2 patients (18%), and reduced amplitude in 2 patients (18%). In one patient, NCS showed no evidence of demyelination, but it did reduced CMAP amplitude in multiple nerves. Despite the complicated interpretation and diagnostic yield, we still believe that they should be the main diagnostic tool for GBS.

Since gadolinium enhanced spinal MRI is known to be a sensitive diagnostic tool, it was performed in 1-9 days from motor symptom onset. Seventy one percent showed nerve root enhancement; even though it was slightly less than the previous studies, it is still supportive^{9,23,32}. Nerve root enhancement was noted as early as one day after the onset of motor symptoms, which may improve diagnostic accuracy. Compared with other conventional studies, this study showed that contrast enhanced MRI appeared to be better for early diagnostic tool than CSF studies. Selective enhancement of the anterior nerve roots has been considered as pathognomonic for GBS, but most of our subjects (>80%) of MRI positive patients revealed enhancement of the anterior and the posterior nerve roots with anterior prominence, regardless of the severity of motor symptoms. One patient demonstrated a diffuse enhancement of aggregated nerve roots of cauda equina and conus medullaris. Furthermore, this study indicates that the positive probability seems to correlate with severity of motor symptoms, even though it is not statistically significant. In this study, duration of enhancement has not been evaluated due to the cost, but serial imaging in one patient revealed complete resolution. We believe that the limitation still exists with gadolinium-enhanced MRI. Nerve root enhancement is not specific for GBS and can occur in other conditions that breakdown integrity of the blood nerve root barrier, such as acquired immune deficiency syndrome, chronic

inflammatory demyelinating polyneuropathy, neoplastic conditions, medications, surgeries, and lumbar puncture^{6,9,33}. However, the majority of these conditions do not form part of the common differential diagnoses in children, and the diagnosis will not be challenging for experienced child neurologists if the clinical and other laboratory findings are taken into consideration. In addition, arranging sedation can be a logistic problem to get MRI studies done in children. Clinicians should weigh the risk versus benefits depending on what kind of settings they practice.

Based on the findings from this study, Gadolinium enhanced spine MRI can be a valuable, additional investigating technique early in the course of GBS, although it does not necessarily replace the main diagnostic tool such as NCS. It can be easily performed at many major hospitals. It allows other potentially devastating conditions to be excluded and the treatment with gamma globulin to be initiated quickly in the earlier course of GBS. In this study, there was no statistically significant difference of severity according to the lesion site or signal intensity. But this study had a limited number of samples. Therefore, further studies are needed to elucidate their clinical values in the management and clinical outcomes.

요약

목적: 길랑-바레 증후군은 소아의 급성 이완성 마비의 가장 흔한 원인 가운데 하나이다. 길랑-바레 증후군은 신경전도 검사와 뇌척수액 검사로 진단하는데 다른 원인과의 감별을 위해 조영증강 척추 자기공명영상 촬영을 시행하기도 한다. 길랑-바레 증후군에서는 자기공명영상 상에서 신경근의 조영증강 소견을 보여 자기공명영상 검사가 진단에 도움을 주기도 한다. 따라서 본 연구는 소아의 길랑-바레 증후군의 진단에 있어 뇌척수액검사와 신경전도검사를 이용한 진단과 비교하여 자기공명영상 검사의 임상적 유용성을 평가하고자 하였다.

방법: 2009년 6월부터 2014년 6월까지 길랑-바레 증후군으로 경북대학교병원에 입원한 17명의 환아를 대상으로 후향적 연구를 시행하였다. 면역글로불린의 치료 전에 뇌척수액검사를 시행하였으며 급성기 동안 신경전도검사를 시행하였다. 모든 환아에서 조영증강 척추 자기공명영상 검사를 시행하였다.

결과: 운동증상 발생 후 뇌척수액검사는 증상 발생 후 평균 3일에 시행하였으며 2명(11%)만이 단백세포해리를 보였으며 신경전도검사는 증상 발생 후 평균 7일에 시행하였으며 12명(71%)에서 양성을 나타냈다. 조영증강 척추 자기공명영상 검사는 증상 발생 후 평균 4일에 시행하였으며 12명(71%)의 환아가 신경근의 조영증강을 보였다. 길랑-바레 증후군에서는 전근에서 조영증강이 특이소견인데 이 환아들은 전근의 조영증강 우세를 동반하여 전근과 후근 모두에서 조영증강 소견을 보였다. 뇌척수액검사와 신경전도검사와 비교할 때 조영증

강 자기공명영상 검사는 뇌척수액검사에 비해 더 높은 양성률을 보여 길랑-바레 증후군의 진단에 있어 더 유용한 방법임을 보여주었으며 ($P=0.0013$) 증상 정도에 따라 척수 전근에서 조영증강의 차이를 보였으나 통계학적인 의미는 없었다($P=1.0$). 검사의 양성확률 또한 운동 증상의 심한 정도와 관계가 있었으나 통계적으로 유의한 차이는 보이지 않았다($P=0.29$).

결론: 본 연구에서 길랑-바레 증후군의 진단시에 뇌척수액검사와 비교하여 조영증강 척추 자기공명영상 검사가 양성 확률이 더 높으며 자기공명영상에서 조영증강을 나타낸 경우 증상의 심한 정도에 따라 조영의 차이를 보였으나 통계학적인 의미는 없었다. 따라서 길랑-바레 증후군의 조기진단에 있어 조영증강 척추 자기공명영상 검사는 유용한 검사방법이 될 수 있을 것이다.

References

- Hicks CW, Kay B, Worley SE, Moodley M. A clinical picture of Guillain-Barre syndrome in children in the United States. *J Child Neurol* 2010;25:1504-10.
- Vucic S, Kiernan MC, Cornblath DR. Guillain-Barre syndrome: an update. *J Clin Neurosci* 2009; 16:733-41.
- Rosen BA. Guillain-Barre syndrome. *Pediatr Rev* 2012;33:164-70; quiz 170-1.
- Ryan MM. Guillain-Barre syndrome in childhood. *J Paediatr Child Health* 2005; 41:237-41.
- Gupta D, Nair M, Baheti NN, Sarma PS, Kuruvilla A; Diplomate-American Board. Electrodiagnostic and clinical aspects of Guillain-Barre syndrome: an analysis of 142 cases. *J Clin Neuromuscul Dis* 2008; 10:42-51.
- Smith N, Pereira J, Grattan-Smith P. Investigation of suspected Guillain-Barre syndrome in childhood: what is the role for gadolinium enhanced magnetic resonance imaging of the spine? *J Paediatr Child Health* 2014;50:E72-6.
- Cerisola-Cardoso A, Capote-Moreira G, Scavone-Mauro C. Guillain-Barre syndrome in paediatrics. Different forms of presentation and difficulties involved in reaching an early diagnosis. *Rev Neurol* 2007; 44:725-32.
- Alkan O, Yildirim T, Tokmak N, Tan M. Spinal MRI findings of guillain-barre syndrome. *J Radiol Case Rep* 2009; 3:25-8.
- Mulkey SB, Glasier CM, El-Nabbout B, Walters WD, Ionita C, McCarthy MH, et al. Nerve root enhancement on spinal MRI in pediatric Guillain-Barre syndrome. *Pediatr Neurol* 2010; 43:263-9.
- Zhang HL, Yang Y, Zhou HW, Wu J. Enhanced magnetic resonance imaging of Guillain-Barre syndrome. *J Paediatr Child Health* 2011;47: 575.
- Hughes RA, Newsom-Davis JM, Perkin GD, Pierce JM. Controlled trial prednisolone in acute polyneuropathy. *Lancet* 1978; 2:750-3.
- Albers JW, Donofrio PD, McGonagle TK. Sequential electrodiagnostic abnormalities in acute inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve* 1985; 8:528-39.
- Hadden RD, Cornblath DR, Hughes RA, Zielasek J, Hartung HP, Toyka KV, et al. Electrophysiological classification of Guillain-Barre syndrome: clinical associations and outcome. Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. *Ann Neurol* 1998; 44:780-8.
- Barisic N, Grkovic L. Long term clinical and electrophysiological assessment of Croatian children with corticospinal tract involvement in Guillain-Barre syndrome (GBS). *Eur J Paediatr Neurol* 2010;14:391-9.
- Dididze MN. Clinical variants of Guillain-Barre syndrome: some aspects of differential diagnosis. *Georgian Med News* 2009; (166):48-51.
- Gorson KC, Ropper AH. Nonpoliovirus poliomyelitis simulating Guillain-Barre syndrome. *Arch Neurol* 2001; 58:1460-4.
- Hosokawa M, Arai T, Yamashita M, Tsuji H, Nonaka T, Masuda-Suzukake M, et al. Differential diagnosis of amyotrophic lateral sclerosis from Guillain-Barre syndrome by quantitative determination of TDP-43 in cerebrospinal fluid. *Int J Neurosci* 2014; 124:344-9.
- Islam Z, Jacobs BC, van Belkum A, Mohammad QD, Islam MB, Herbrink P, et al. Axonal variant of Guillain-Barre syndrome associated with Campylobacter infection in Bangladesh. *Neurology* 2010;74:581-7.
- Martens-Le Bouar H, Korinthenberg R. Polyradiculoneuritis with myelitis: a rare differential diagnosis of Guillain-Barre syndrome. *Neuropediatrics* 2002; 33:93-6.
- Odaka M, Yuki N. Variants and differential diagnosis of Guillain-Barre syndrome. *Expert Rev Neurother* 2002; 2:877-89.
- Randall DP. Guillain-Barre syndrome differential diagnosis. *Dis Mon* 2010; 56:266-78.
- Shaikh AG, Termsarasab P, Nwankwo C, Rao-Frisch A, Katirji B. Atypical forms of Guillain-Barre syndrome and H1N1-influenza vaccination. *Vaccine* 2012; 30:3251-4.
- Yikilmaz A, Doganay S, Gumus H, Per H, Kumandas S, Coskun A. Magnetic resonance imaging of childhood Guillain-Barre syndrome. *Childs Nerv Syst* 2010;26:1103-8.
- Zhang HL, Wang JM, Zhou HW, Xu J, Wu J. Magnetic resonance imaging of Guillain-Barre syndrome. *Childs Nerv Syst* 2010;26:1135; author reply 1137.
- Erazo Torricelli R. Guillain Barre syndrome in pediatrics. *Medicina (B Aires)* 2009; 69:84-91.
- Burns TM. Guillain-Barre syndrome. *Semin Neurol* 2008; 28:152-67.
- Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R. Guillain-Barre syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2011; 29:599-612.
- Mateen FJ, Cornblath DR, Jafari H, Shinohara RT, Khandit D, Ahuja B. Guillain-Barre Syndrome in India: population-based validation of the Brighton criteria. *Vaccine* 2011;29:9697-701.
- Yuki N, Hartung HP. Guillain-Barre syndrome. *N Engl J Med* 2012; 366:2294-304.
- Olney RK, Aminoff MJ. Electrodiagnostic features of the Guillain-Barre syndrome: the relative sensitivity of different techniques.

- Neurology 1990; 40:471-5.
- 31) Vucic S, Cairns KD, Black KR, Chong PS, Cros D. Neurophysiologic findings in early acute inflammatory demyelinating polyradiculoneuropathy. Clin Neurophysiol 2004; 115:2329-35.
- 32) Byun WM, Park WK, Park BH, Ahn SH, Hwang MS, Chang JC. Guillain-Barre syndrome: MR imaging findings of the spine in eight patients. Radiology 1998; 208:137-41.
- 33) Yikilmaz A, Doganay S, Gumus H, Per H, Kumandas S, Coskun A. Magnetic resonance imaging of childhood Guillain-Barre syndrome. Childs Nerv Syst 2010; 26:1103-8.