ORIGINAL ARTICLE

Sonoelastographic Evaluation of Medial Gastrocnemius Muscles Intrinsic Stiffness After Rehabilitation Therapy With Botulinum Toxin A Injection in Spastic Cerebral Palsy

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ABSTRACT. Park G-Y, Kwon DR. Sonoelastographic evaluation of medial gastrocnemius muscles intrinsic stiffness after rehabilitation therapy with botulinum toxin A injection in spastic cerebral palsy. Arch Phys Med Rehabil 2012;93:2085-9.

Objective: To investigate intrinsic stiffness changes using real-time sonoelastography (RTS) in the medial gastrocnemius muscle (GCM) after rehabilitation therapy with botulinum toxin type A (BTA) injection in spastic cerebral palsy (CP).

Design: Prospective study using ultrasonography and RTS.

Setting: An inpatient rehabilitation clinic.

Participants: Children (N=17) with spastic CP (mean age, 57±22y, age range, 26–110mo).

Intervention: Rehabilitation therapy and intramuscular injection of BTA in both medial and lateral GCMs.

Main Outcome Measures: RTS was obtained on the medial GCM, and the elastic pattern of the medial GCM was graded from RTS 1 (purple to green: soft) to RTS 4 (red: stiff) on the basis of color-scaled RTS. RTS score, color histogram, Modified Ashworth Scale (MAS) score of the ankle plantar flexor muscles, and Gross Motor Function Measure (GMFM) score were obtained before intervention and 4 weeks after intervention. The correlations among RTS score, GMFM, and MAS score were determined. Intrarater reliability was also evaluated.

Results: Before and at 4 weeks after intervention, the mean RTS score decreased from 3.4 to 1.5 ($P<.05$), median red pixel intensity decreased from 112.5 to 101.3 ($P<.05$), median blue pixel intensity increased from 82.6 to 90.4 ($P<.05$), mean MAS score of the ankle decreased from 2.7 to 1.3 ($P<.05$), and mean GMFM score increased from 54.55% to 62.32%. Significant correlations were observed between the RTS score and the MAS score. Intrarater reliability was high.

Conclusions: Our results suggest that more information about the change of spastic muscle in CP after rehabilitation treatment with BTA may be gained by estimating muscle stiffness using RTS combined with clinical scale measurements.

Key Words: Cerebral palsy; Gastrocnemius muscle; Muscle spasticity; Rehabilitation; Sonoelastography.

CEREBRAL PALSY (CP) is a group of disorders associated with the maldevelopment of movement and posture caused by damage to the brain before, during, or shortly after birth. The spasticity caused by CP can be a very disabling feature, including limited locomotor ability, joint contracture, and many problems performing daily tasks. A wide range of therapeutic procedures such as physical modalities, oral pharmacologic agents, peripheral neuromuscular blockades, intrathecal agents, and surgical intervention have been applied to manage spasticity.[1]

Botulinum toxin type A (BTA) is a recently well-documented, safe, and noninvasive adjunct to manage children with spastic CP.[2] BTA provides an effective, short-term intervention to reduce spasticity. Moreover, the relaxation of spastic muscles facilitates limb growth and reduces the development of fixed contractures.[3,4]

A precise evaluation of spasticity is important to establish the effectiveness of medical and physical therapeutic interventions. Various diagnostic methods are available to investigate specific influences on muscles. The most obvious diagnosis of spasticity is based on clinical assessments of muscle tone by a physician or physiotherapist, such as the Modified Ashworth Scale (MAS)[5] and the Modified Tardiue Scale. The spasticity has the neural component that is evoked by a velocity-dependent phenomenon and the biomechanical component such as soft-tissue compliance, that is, stiffness, together.[6] The muscle hyperactivity seen in the spastic muscle results in muscle stiffness and spasm.[7] One of the most relevant parameters used to quantify stiffness (or elasticity) of soft tissue is Young's (or elastic) modulus.[8]

Real-time sonoelastography (RTS) is a recently developed ultrasound-based technique that evaluates tissue elasticity in real time. RTS is based on the principle that tissue compression produces strain (displacement), which is lower in hard tissue and higher in soft tissue.[9] We previously reported that RTS demonstrated difference in muscle stiffness between spastic and normal gastrocnemius muscle (GCM) in CP.[10] Few studies have evaluated the change in muscle stiffness using RTS in children with spastic CP after intervention. Therefore, we evaluated changes in GCM stiffness after rehabilitation therapy with BTA injection in children with spastic CP using RTS.

List of Abbreviations

BTA	botulinum toxin type A
CP	cerebral palsy
GCM	gastrocnemius muscle
GMFM	Gross Motor Function Measure
ICC	intraclass correlation coefficient
MAS	Modified Ashworth Scale
ROI	region of interest
RTS	real-time sonoelastography

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METHODS

Participants

Seventeen children (10 boys and 7 girls; mean age ± SD, 57±22mo [age range, 26–110mo]; 12 with diplegia and 5 with hemiplegia; mean body weight, 12.5kg [range, 11–15kg]) were admitted to the inpatient clinic of the Department of Rehabilitation Medicine at Daegu Catholic University Medical Center. Inclusion criteria were as follows: (1) diagnosis of CP verified by a physiatrist who was a specialist in pediatric rehabilitation medicine, (2) ability to ambulate independently with or without assistive devices, (3) spastic gait with equinus of the ankle, and (4) revealed dynamic contracture of a spastic ankle. The dynamic contracture of the ankle was defined if the equinus of the ankle was observed during ambulation and passive dorsiflexion of the ankle could be accomplished beyond the neutral position with the knee fully extended. Exclusion criteria were as follows: (1) age above 13 years and below 2 years, (2) previous BTA injection to the GCMs or serial casting of the ankle within 6 months before enrollment, (3) fixed ankle contracture, or (4) previous surgery on the lower limbs. The institutional review board and ethics committee at Daegu Catholic University Medical Center approved this study protocol. Because all the children in this study were younger than 18 years, informed consent was obtained from the parents of the children for their participation in the study.

Procedures

All the children received an intramuscular injection with mean BTA (Botox) 20 U (range, 16–23U, 1.5U/kg) to each medial and lateral GCM under ultrasound guidance. No side effects or complications were observed after the injection. Before the BTA injection, all the children had undergone outpatient rehabilitation treatment once a week. After the BTA injection, inpatient rehabilitation treatment including stretching and strengthening exercises, functional electrical stimulation, and progressive gait training was performed twice a day for 4 weeks.

Clinical and ultrasound assessments were performed at preintervention and at 4 weeks postintervention. The spasticity of ankle plantar flexor muscles in children with spastic CP was measured as the degree of resistance to passive movement using MAS and rated from 0 (normative) to 5 (extreme) according to the amount of resistance felt by the physical therapist. The physical therapist also measured the Gross Motor Function Measure (GMFM) score.

B-mode ultrasound and RTS of the medial GCM were performed together using the commercially available ultrasound system with a 5- to 13-megahertz multifrequency linear transducer[a] by a physiatrist with 17 years of musculoskeletal ultrasound experience and 4 years of RTS experience. B-mode ultrasound and RTS were scanned on the longitudinal plane of the medial GCM, and minimal compression was applied with the transducer weight during the children's respiration. All children were scanned in the prone position with feet hanging from the edge on an examination table. Scanning was discontinued whenever reflexive or voluntary contraction of the lower limb muscles was visually apparent. The proximal tendon, musculotendinous junction, and muscle of medial GCM were sequentially identified from proximal to distal scanning of the leg, and the medial GCM was easily distinguished from the other muscles on ultrasound. After that, ultrasound and RTS were repeatedly performed at the fixed point of the medial GCM, which was located at the middle of 2 reference points (1 point was located at the proximal one third of a longitudinal line from midway between the medial and lateral malleoli to midway between the medial and lateral epicondyles; the other point was located at the medial end on a transverse line perpendicular to the point on the longitudinal line). Using the B-mode ultrasound display for guidance, a region of interest (ROI) was selected that included the medial GCM fascicles, clearly demarcated linear hyperechoic strands related to fibroadipose septa (perimysium), and normal surrounding tissue.

The RTS scan was a color-coded graphic representation of the relative stiffness of structures within the selected ROI, such that purple indicated soft, green and yellow indicated intermediate stiffness, and red indicated stiff. An appropriate degree of natural compression was determined by manual adjustment, such that the perimysium appeared predominantly yellow to red on RTS. Color-coded RTS was depicted on the left side of the screen, whereas the B-mode ultrasound image was displayed on the right side. Our protocol included standardized color encoding, and the same color scale was used for all children.

The recorded sonoelastographic images were replayed to select the best representative image, which was defined as adequate depiction of tissue structure and consistent reproduction of the scanned images. The elastic pattern in the medial GCM was graded semiquantitatively by the physiatrist as follows: 1 (purple to green: soft), 2 (green to yellow), 3 (yellow to red), and 4 (red: hard)[11] (table 1). In addition, the color pattern of the recorded images was quantitatively analyzed on a personal computer using Image J software[b] by the other physiatrist. The ROI was set to cover the entire GCM, excluding the hyperechoic perimysium. The color of the pixels ranged from 0 to 255.

The color histogram represents the number of pixels that have colors in each of a fixed list of color ranges and calculates the intensity of each color component of the pixels within the ROI. The higher value was defined as greater color intensity. Median blue and red pixel intensities were obtained on the color histogram for the analysis. RTS scanning was performed twice, and 2 representative RTS images were taken in each scan to check the intrarater reliability of the RTS score and color pixel intensity.

Statistical Analysis

The statistical analysis was performed using SPSS 14.0,[c] with the level of significance set at $<.05$. The Wilcoxon signed-rank test was used to assess differences pre- and postintervention. The relationship between RTS scores and clinical evaluation scores was determined with Spearman's rank correlation test. The intraclass correlation coefficient (ICC) was used to examine intrarater reliability of repeated RTS scores and color pixel intensity measurements.

RESULTS

The ICC of the repeated RTS score measurements in pre- and postintervention was .855 and .878, respectively. The mean

Table 1: Sonoelastography Scoring System for Medial GCM

RTS Score	Interpretation	Sonoelastographic Appearance
1	Soft	Purple or green in ROI
2	Mostly soft	Green or yellow and <10% small areas of red in ROI
3	Mostly hard	Red and yellow areas in nearly same distribution in ROI
4	Hard	Predominantly red and <10% small areas of green in ROI

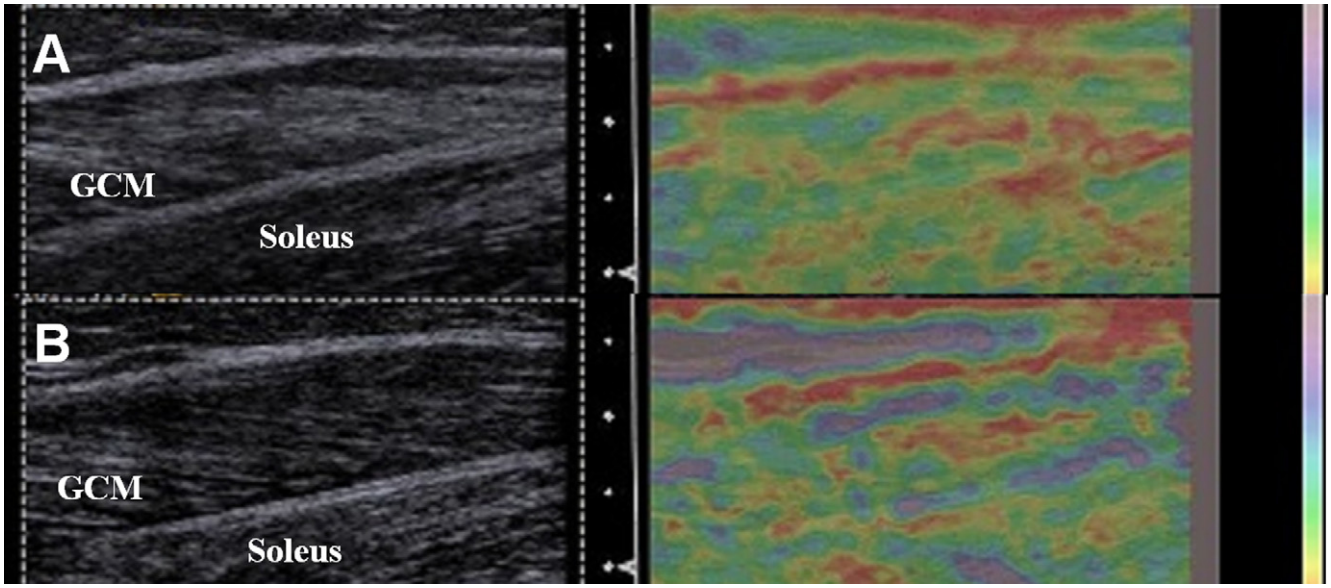

Fig 1. RTS image presentation of local muscle stiffness superimposed on the longitudinal B-mode ultrasound image of right medial gastrocnemius muscle. (A) RTS image (right) showed yellow to red coloring before rehabilitation therapy with BTA injection. (B) RTS image (right) of the spastic medial GCM showed purple to green coloring at 4 weeks of rehabilitation therapy with BTA injection.

RTS score of the GCM before and at 4 weeks after intervention decreased significantly from 3.4 to 1.5 ($P<.05$) (fig 1). The ICC of the repeated color pixel intensity measurements in pre- and postintervention was .906 and .912 for red and .915 and .926 for blue, respectively. The median red pixel intensity of the hard area decreased from 112.5 to 101.3 ($P<.05$) (fig 2), and the median blue pixel intensity of the soft area increased from 82.6 to 90.4 ($P<.05$) (see fig 2). The mean MAS score of the ankle plantar flexor muscles showed improvement from grade 2.7 to grade 1.3 ($P<.05$) (table 2). Mean GMFM score also improved from 54.55% at baseline to 62.32% 1 month after the intervention (see table 2). RTS score was positively correlated with median red pixel intensity in the medial GCM ($\rho=.756$) and negatively correlated with median blue pixel intensity ($\rho=.605$). The MAS score was positively correlated with the RTS score ($\rho=.778$). No correlation was found between the RTS score and the GMFM score.

DISCUSSION

Our results showed that rehabilitation therapy with BTA injection resulted in a short-term reduction in muscle spasticity, which was demonstrated by a decrease in the MAS score from grade 2.7 to grade 1.3 and decreased muscle stiffness through RTS at 4 weeks after the intervention. Clinically, gross hard calf muscles showed a change to soft muscles with less stiffness. A previous study[12] showed that spastic muscle cells have shorter resting sarcomeres and an increased elastic modulus compared with those in normal muscle cells, suggesting dramatic remodeling of intra- and extracellular structural components such as titin and collagen. Animal study on hereditary spastic mice showed that BTA injected into the calf muscles at 6 days of life has a significant impact on muscle length. Untreated muscles of the spastic mice were 16% shorter than those of normal siblings, whereas treated mice had muscle lengths within 2% of normal mice.[4]

Spasticity consists of 2 major components. Neural component is the level of resistance on passive movement and evoked by a velocity-dependent phenomenon. Biomechanical component, which means muscle stiffness, consists of high collagen content in spastic muscle. Collagen content increases in the spastic muscles of children with CP, and the MAS score is significantly correlated with the amount of total collagen in spastic muscle.[13] Because RTS measures the stiffness of spastic muscle, increased collagen content in spastic muscle was indirectly estimated using RTS. Our results revealed the significant correlation between the RTS score and the MAS score.

In our study, no correlation was found between the RTS score and the GMFM score. We can suggest several reasons for this discrepancy. First, children's gross motor function is more associated with motor control than muscle tone.[14,15] Second, clinical assessments were performed at 4 weeks after injection in our study. The GMFM is a standard, validated instrument that was developed specifically for children with CP and was designed to detect quantitative changes in gross motor function. Although the GMFM is considered 1 of the best available tools, it may not be sensitive enough to evaluate the effects of short-term treatment in children with mild to moderate disability.[16]

Third, we did not contemplate the influence of children's age in the assessment of gross motor function. While young children with CP tend to get the therapeutic effect from BTA injection, GMFM is recommended for children whose age is older than 5 years.[16] In our study, 10 of the 17 children were younger than 5 years. Therefore, this discrepancy may limit an exact measurement of functional improvement in young children. Last, children with severe disability may not have measurable change on the GMFM score despite subjectively perceived improvement after BTA injection.

It is important to note the limitations of this study. Children were evaluated for only 4 weeks, so longer follow-up studies are needed to provide more information to clinicians for managing and observing changes in children with spastic CP. Because of the nature of the treatment technique, double blinding, as well as blinding of the children or examiner, was not considered feasible in this study.

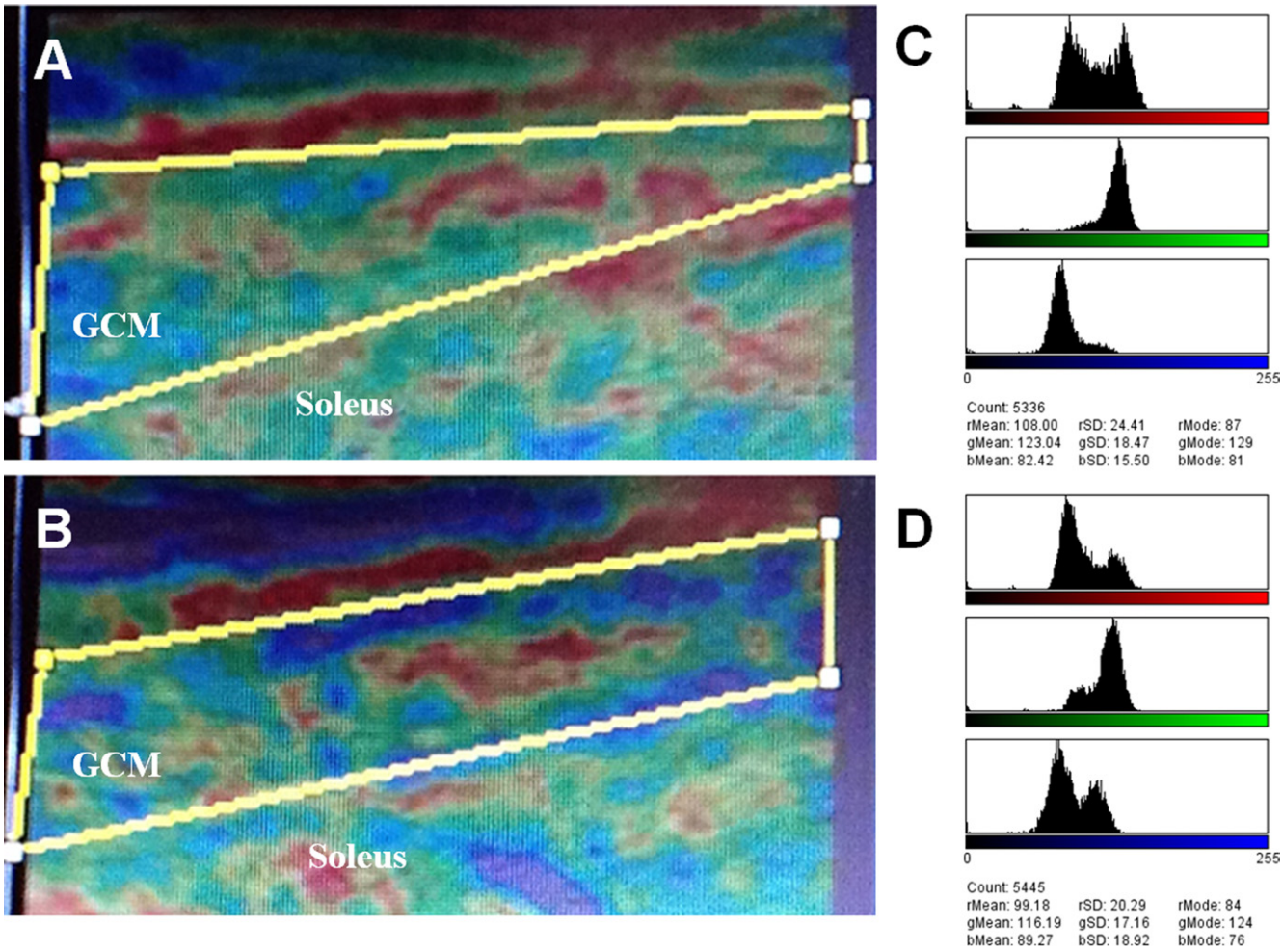

Fig 2. Longitudinal RTS image and color histogram of spastic medial GCM. Yellow polygons depict ROI area of quantitative analysis of the medial GCM on color histogram. In spastic medial GCM before rehabilitation therapy with BTA injection, (A) RTS image showed yellow to red coloring and (B) the mean values for the intensity of red and blue on color histogram were 108.0 and 82.4, respectively. In spastic medial GCM at 4 weeks of rehabilitation therapy with BTA injection, (C) RTS image showed purple to green coloring and (D) the mean values for the intensity of red, green, and blue on color histogram were 99.1, 116.1, and 89.2, respectively.

The results of the present study showed that the reliability of the stiffness changes in the GCM was high. These results are in agreement with those of Nordez et al[17] who showed good reliability of local muscle stiffness at rest using transient elastography in vivo.

Table 2: Summary of Outcome Measures at Pre- and Postintervention of Rehabilitation Therapy With Botulinum Toxin A

Outcome Measures	Preintervention	Postintervention (4wk)
RTS score of right medial GCM	3.4±0.5	1.5±0.5*
Red pixel intensity of right medial GCM†	112.5±4.4	101.3±3.5*
Blue pixel intensity of right medial GCM†	82.6±5.3	90.4±7.2*
MAS of right medial GCM	2.7±0.5	1.3±0.2*
GMFM score (%)	54.5±10.3	62.3±10.7*

NOTE. Values are mean ± SD.
*$P<.05$ from Wilcoxon signed-rank test, pre- vs postintervention.
†Range=0–255.

Study Limitations

RTS has several major limitations due to the technical difficulties. First, we could not evaluate interrater reliability of the RTS parameters according to the sonographer's experience because some children and parents did not adhere to the study protocol. RTS examination is operator-dependent, requires a learning time curve, and has technical problems reproducing images because of the instability of the applied pressure using the freehand technique. The same dynamic RTS results were obtained among RTS score, pixel intensity, and shear wave velocity of medial GCM in the spastic legs of children with CP when the experienced musculoskeletal sonographer performed the dynamic RTS. However, we did not evaluate the difference in the interpretation of RTS results according to the sonographer's experience. Because there is a learning time curve on musculoskeletal ultrasound examination, the same learning time curve could be applied in the interpretation of the RTS results. Second, there is no agreement on the size of the ROI window for RTS. The hardness measurement is influenced by the relative amount of surrounding soft tissue in the window. A larger window tends to include more surrounding soft tissue

and make a hard tissue measure harder. To reduce this variability, we standardized the depth and the width of the window for the medial GCM and soleus. These efforts may have resulted in the good ICC of the repeated RTS score and color pixel intensity measurements.

Finally, RTS is a qualitative not a quantitative assessment. Color histogram analysis of sonoelastographic images is expected to offer an objective index for estimating color-coded graphic representations of the relative stiffness of structures within the selected ROI. Color histogram techniques have been used as part of an effort to increase the objective and quantitative analysis of RTS.

CONCLUSIONS

We identified intrinsic stiffness changes in the GCM after rehabilitation therapy with BTA injection in children with spastic CP using RTS. The results of this study showed that RTS is a valuable tool for detecting structural alterations in the GCM after rehabilitation therapy with BTA injection in the children with spastic CP. Therefore, estimation of tissue stiffness can provide valuable information about characterizing the spastic muscle in the children with spastic CP.

Although larger studies with more subjects and a longer follow-up period are required to confirm the clinical usefulness of RTS, RTS has the potential to become an additional procedure to assess treatment response and accurate muscle architecture.

References

1. Borodic GE, Ferrante R, Pearce LB, Smith K. Histologic assessment of dose-related diffusion and muscle fiber response after therapeutic botulinum A toxin injections. Mov Disord 1994;9:31-9.
2. Ade-Hall RA, Moore AP. Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy. Cochrane Database Syst Rev 2000;2:CD001408.
3. Cosgrove AP, Corry IS, Graham HK. Botulinum toxin in the management of the lower limb in cerebral palsy. Dev Med Child Neurol 1994;36:386-96.
4. Cosgrove AP, Graham HK. Botulinum toxin A prevents the development of contractures in the hereditary spastic mouse. Dev Med Child Neurol 1994;36:379-85.
5. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987;67:206-7.
6. Haugh AB, Pandyan AD, Johnson GR. A systematic review of the Tardieu Scale for the measurement of spasticity. Disabil Rehabil 2006;28:899-907.
7. Ward AB. A summary of spasticity management–a treatment algorithm. Eur J Neurol 2002;9:48-52.
8. Fung YC. Biomechanics: mechanical properties of living tissues. New York: Springer; 1988.
9. Sconfienza LM, Silvestri E, Bartolini B, Garlaschi G, Cimmino MA. Sonoelastography may help in the differential diagnosis between rheumatoid nodules and tophi. Clin Exp Rheumatol 2010;28:144-5.
10. Kwon DR, Park GY, Lee SU, Chung IB. Dynamic sonoelastographic findings of medial gastrocnemius in children with spastic cerebral palsy. Radiology 2012;263:794-801.
11. Park GY, Kwon DR. Application of real-time sonoelastography in musculoskeletal diseases related to physical medicine and rehabilitation: an invited review. Am J Phys Med Rehabil 2011;90:875-86.
12. Fridén J, Lieber RL. Spastic muscle cells are shorter and stiffer than normal cells. Muscle Nerve 2003;27:157-64.
13. Booth CM, Cortina-Borja MJ, Theologis TN. Collagen accumulation in muscles of children with cerebral palsy and correlation with severity of spasticity. Dev Med Child Neurol 2001;43:314-20.
14. Damiano DL, Quinlivan J, Owen BF, Shaffrey M, Abel MF. Spasticity versus strength in cerebral palsy: relationships among involuntary resistance, voluntary torque, and motor function. Eur J Neurol 2001;8:40-9.
15. Molenaers G, Van Campenhout A, Fagard K, De Cat J, Desloovere K. The use of botulinum toxin A in children with cerebral palsy, with a focus on the lower limb. J Child Orthop 2010;4:183-95.
16. Sharp SA, Brouwer BJ. Isokinetic strength training of the hemiparetic knee: effects on function and spasticity. Arch Phys Med Rehabil 1997;78:1231-6.
17. Nordez A, Gennisson JL, Casari P, Catheline S, Cornu C. Characterization of muscle belly elastic properties during passive stretching using transient elastography. J Biomech 2008;41:2305-11.

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