Control of Walking Speed in Children With Cerebral Palsy

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Background: Children's ability to control the speed of gait is important for a wide range of activities. It is thought that the ability to increase the speed of gait for children with cerebral palsy (CP) is common. This study considered 3 hypotheses: (1) most ambulatory children with CP can increase gait speed, (2) the characteristics of free (self-selected) and fast walking are related to motor impairment level, and (3) the strategies used to increase gait speed are distinct among these levels.

Methods: A retrospective review of time-distance parameters (TDPs) for 212 subjects with CP and 34 typically developing subjects walking at free and fast speeds was performed. Only children who could increase their gait speed above the minimal clinically important difference were defined as having a fast walk. Analysis of variance was used to compare TDPs of children with CP, among Gross Motor Function Classification System (GMFCS) levels, and children in typically developing group.

Results: Eight-five percent of the CP group (GMFCS I, II, III; 96%, 99%, and 34%, respectively) could increase gait speed on demand. At free speed, children at GMFCS I and II were significantly faster than children at GMFCS level III. At free speed, children at GMFCS I and II had significantly greater stride length than those at GMFCS levels III. At free speed, children at GMFCS level III had significantly lower cadence than those at GMFCS I and II. There were no significant differences in cadence among GMFCS levels at fast speeds. There were no significant differences among GMFCS levels for percent change in any TDP between free and fast walking. Discussion: Almost all children with CP at GMFCS levels I and II can control the speed of gait, however, only one-third at GMFCS III level have this ability. This study suggests that children at GMFCS III level can be divided into 2 groups based on their ability to control gait speed; however, the prognostic significance of such categorization remains to be determined. Level of Evidence: Diagnostic level II.

Key Words: cerebral palsy, gait velocity, control

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Children's ability to control the speed of their gait is important for a wide range of functional activities, including the ability to "keep up" with their peers. For

typically developing (TD) children, there is a linear relationship between speed, stride length, and cadence.¹⁻⁶ Increased speed of gait is usually accomplished by in-creasing both stride length and cadence.^{7–9} It is thought that the ability to increase the speed of gait for children with cerebral palsy (CP) is "common."10-12 Previous study suggest that these children utilize distinct mechanisms for increasing gait velocity, relying on preferentially increasing cadence, and having relatively limited ability to increase stride length.¹² The few studies on this issue are limited by small sample sizes, imperfect classification of subjects, and imprecise calculation and definition of significant changes in gait velocity. In addition, clinicians have speculatively correlated the ability to increase gait speed on demand with the magnitude of disability, presuming that children with the ability to control the speed of their gait have less motor impairment than those who cannot control their gait speed, and that the former are better candidates for single-event multilevel surgery (SEMLS) to improve gait.^{10,11,13} This has been particularly applied to clinical decision making for children who ambulate at the Gross Motor Function Classification System (GMFCS) level III (ie, require assistive devices for ambulation), in which the outcomes following SEMLS are less predictable.^{14–21}

The ability to control gait velocity has long been an interest in the Motion Analysis Laboratory (MAL) at our institution, following the development of a gait graph that relates speed, stride length, cadence, body height, age, and sex for TD children walking over a range of speeds.²² As a result, children with CP evaluated in the laboratory are routinely tested at free (self-selected) and fast walking speeds. A retrospective case series was performed, comparing free and fast walking time-distance parameters (TDPs) in these children, utilizing a validated classification of motor impairment (ie, the GMFCS) and more precise definition of change in gait velocity [the minimal clinically important difference (MCID)].^{23,24} The study was designed to consider 3 hypotheses: (1) most ambulatory children with CP can increase their gait velocity, (2) the TDP characteristics of free and fast walking are related to motor impairment level, as reflected by the GMFCS, and (3) the strategies used to increase gait speed are distinct among GMFCS levels.

METHODS

The study design was a diagnostic study, retrospective case series, resulting in level II evidence. The data were part of a single-site study that was approved by our

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Institutional Review Board and granted a waiver of informed consent and Health Insurance Portability and Accountability Act authorization for research. Subjects were identified for recruitment based on referral to the MAL for gait analysis. Inclusion criteria consisted of individuals between the ages of 6 and 20 years with a diagnosis of CP, clinician-determined GMFCS level I, II, or III, complete quantitative gait analysis study, and no pharmacologic or surgical interventions within 6 months before the index study. A complete gait study included a physical examination by a physical therapist or kinesiologist, and recorded TDP, kinematics, kinetics, and dynamic electromyography at free and fast speeds. For the fast walk the patients were instructed to walk as fast as they could without running and without falling. Selection of a representative fast walk was performed based upon assessment of reproducibility of time-distance parameters (ie, speed, stride length, and cadence). Within these guidelines, instability, stumbling, and falling during the fast walk trials did not occur. None of the children at the GMFCS III level used orthoses that extended proximal to the knee. Self-selected and fast walk trials for this group were identical with respect to the use of orthoses and assistive devices. Individuals were excluded if they were classified as GMFCS level IV or V, or GMFCS levels I to III with an incomplete quantitative gait analysis study (usually due to cognitive issues), or had pharmacologic or surgical interventions within the previous 6 months. For comparison, a group of TD children between the ages of 5 and 20 years were recruited for comparable study in the MAL.

Data extracted from the medical record of each participant included patient clinical history, demographic information (medical record number, patient name, date of birth, ethnicity, sex, diagnosis, and GMFCS level. MAL patient records were also reviewed and time-distance parameters were extracted for study purposes.

Only children who could increase gait speed above the MCID were defined as having a fast walk for analyses comparing TDPs among TD and CP (subdivided by

GMFCS level) groups. Children in the TD group were defined as having a fast walk for analyses if they could increase gait speed above the MCID designated for GMFCS level I. Time-distance parameters were normalized to age at time of study. Percent change in speed between free and fast walking trials were calculated for each subject and compared with the MCID of medium (0.5)effect size defined for each GMFCS level (8.7% for level I, 6.8% for level II, and 5.5% for level III).²⁴ Percent change in stride length between free and fast walks were calculated for each subject and compared with the MCID of medium (0.5) effect size defined for each GMFCS level (4.2% for level I, 3.9% for level II, and 4.9% for level III).²⁴ Percent change in cadence between free and fast walks were calculated for each subject and compared with the MCID of medium (0.5) effect size defined for each GMFCS level (5.9% for level I, 7.6% for level II, and 5.2% for level III).²⁴ Percent change in stride length of children in the TD group were compared with the designated MCID for GMFCS level I.

One-way analysis of variance with the Bonferroni post hoc testing was performed to explore the differences among the TD and GMFCS groups at free and fast walking speeds. A significance level of $P \le 0.05$ and a confidence interval at 95% were used for all statistical comparisons. Data are presented as means and SDs, unless otherwise indicated.

RESULTS

Cohort Demographics

There were 212 subjects who met the inclusion criteria for the CP group, and 34 subjects in the TD group, and their demographics are summarized in Table 1. There were 119 males and 93 females in the CP group. Mean age was 13.1 years (6.2 to 19.3 y, SD = 3.2 y). In the TD group, there were 15 males and 19 females, with a mean age of 10.6 years (range, 5.1 to 16.6 y, SD = 3.2 y). Distributions of number of subjects, sex distribution, and mean age, height, and weight for GMFCS levels I to III are shown in Table 1. Children at GMFCS I were

TABLE 1. TD and CPCohort Demographic	GMFCS I	GMFCS II		· · ·		
Parameters	(n = 80)	(n = 91)	GMFCS III $(n = 41)$	TD (n = 34)	Р	Group Differences§ (P)
Age (SD) (y)*	13.8 (2.8)	12.2 (3.2)	13.8 (3.5)	10.6 (3.2)	< 0.001‡	I vs. II (0.004), I vs. TD (< 0.001); III vs. II (0.041); III vs. TD (< 0.001)
Age range (y)	8.7-19.2	6.2-18.4	7.3-19.3	5.1-16.6		
Sex distribution	44 M; 36 F	50 M; 41 F	25 M; 16 F	15 M; 19 F	0.535†	
Height (SD) (cm)*	152.5 (13.1)	144.7 (15.9)	145.5 (17.2)	144.2 (20.7)	0.006‡	I vs. II (0.01)
Height range (cm)	126-179	104-174	115-174	111-187		
Weight (SD) (kg)*	49.8 (17.0)	42.6 (15.6)	44.2 (14.9)	42.6 (19.1)	0.025‡	I vs. II (0.029)
Weight range (kg)	25.0-104.1	16.7-85.0	20.0-79.0	18.2-102.8		
Diplegia/hemiplegia CP	36/44	64/27	41/0	0/0		

*Values are reported as mean and SD.

 $\dagger \chi^2$, cross-table GMFCS and sex.

 \tilde{P} -value is the significance of the F ratio for the analysis of variance between groups.

§Group differences indicate results of post hoc Bonferroni comparison.

CP indicates cerebral palsy; F, female; GMFCS, Gross Motor Function Classification System; M, male; TD, typically developing.

significantly older (P = 0.004), taller (P = 0.01), and heavier (P = 0.029) than children at GMFCS level II. Children at GMFCS I were also older than those in the TD group (P < 0.001). Children at GMFCS III were significantly older than those in the TD group and at GMFCS level II (P < 0.001 and P = 0.041, respectively). χ^2 testing demonstrated no differences in sex distribution among TD and CP (by GMFCS). Sixty-three of 80 (79%) subjects at the GMFCS I level had no previous surgery. For subjects at the GMFCS II level, 80/91 (88%) had no previous surgery. For those at the GMFCS III level, 32/41 (78%) had no previous surgery.

Ability to Increase Gait Speed Above MCID

Analysis of the cohort's ability to significantly increase gait speed on demand is summarized in Figure 1. One hundred eighty-one of the 212 children with CP (85%) were able to significantly increase gait speed above MCID. The mean increase in speed for these children with CP was 44% (range, 8.7% to 100.3%, SD = 18.2%). Seventy-seven of 80 children (96%) at GMFCS I level were able to significantly increase gait speed. At the GMFCS I level, 42/44 (95%) subjects with hemiplegic-type CP were able to increase walking speed above MCID threshold. Similarly, 35/36 (97%) subjects with diplegic-type CP were able to increase walking speed above MCID threshold.

The mean increase in speed for these children at GMFCS I was 44% (range, 8.9% to 100.3%, SD = 18.5%). Ninety of 91 children (99%) at GMFCS II level were able to significantly increase gait speed. At the GMFCS II level, 26/27 (96%) subjects with hemiplegic-type CP were able to increase walking speed above MCID threshold. All of the 64 (100%) subjects with diplegic-type CP were able to increase walking speed above MCID threshold. The mean increase walking speed above MCID threshold. The mean increase

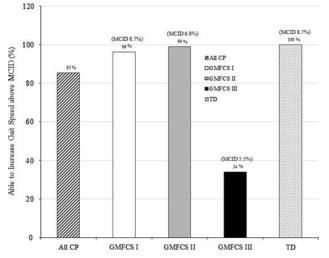


FIGURE 1. Histogram comparing the percentage of children in typically developing (TD) and cerebral palsy (CP) groups [Gross Motor Function Classification System (GMFCS) I, II, III] who increased gait speed above the minimal clinically important difference (MCID), shown in parentheses, designated for each group. The MCID defined for GMFCS I was used for the TD group.

in speed for these children at GMFCS II was 43% (range, 8.7% to 83.8%, SD = 17.3%). However, only 14 of 41 subjects (34%) at GMFCS III level were able to significantly increase gait speed. For these 14 subjects at GMFCS III, the mean increase in speed was 44% (range, 20.4% to 88.6%, SD = 22.8%). Of the 14 patients at the GMFCS III level who could increase gait speed, 11 (79%) had no previous surgery. Of the 27 patients at the GMFCS III who could not increase gait speed, 21 (78%) had no previous surgery. Thirty four of 34 children (100%) in the TD group were able to significantly increase gait speed using the MCID defined for GMFCS level I. Children in the TD group had a mean increase in speed of 54.2% (range, 17.7% to 113.1%, SD = 21.8%).

Characteristics of Free and Fast Walking

Analysis of the characteristics (speed, stride length, and cadence) of free and fast speeds by TDs and GMFCS levels is summarized in Table 2 and Figure 2. It should be noted that 80 children at GMFCS I, 91 at GMFCS II, and 41 at GMFCS III performed free walks, whereas only 77 children at GMFCS I, 90 at GMFCS II, and 14 at GMFCS III completed fast walks. All 34 children in the TD group were able to perform both free and fast walks. Significant differences were noted among GMFCS levels and TDs for free and fast walking speed, stride length, and cadence. At free speed, the TD group had significantly greater speed and stride length than all the GMFCS level groups (P < 0.001). TD cadence was significantly greater than GMFCS III level only (P = 0.006). At free speed among GMFCS groups, both GMFCS levels I and II had significantly greater speed, stride length, and cadence than the GMFCS III group (P < 0.001). There were no differences in free speed timedistance parameters between GMFCS levels I and II. At fast speed, the TD group had significantly greater speed and stride length than all the GMFCS level groups (P < 0.001). TD group cadence was not significantly different from any of the GMFCS groups. At fast speed among GMFCS groups, GMFCS level I had significantly greater speed and stride length than GMFCS III (P < 0.001), and significantly greater stride length than GMFCS level II (P = 0.005). There were no significant differences in cadence among GMFCS groups.

Strategies Used to Increase Gait Speed

Analysis of the strategies used to increase gait speed by GMFCS level, expressed as the mean percent difference in speed, cadence, and stride length going from free to fast walks, is summarized in Table 3 and Figure 3. The mean increase in speed for children at GMFCS I was 44% (8.9% to 100.3%, SD = 18.5%), at GMFCS II was 44% (8.7% to 83.8%, SD = 17.3%), and at GMFCS III was 44% (20.4% to 88.6%, SD = 22.8%). Children in the TD group had a mean increase in speed of 54.2% (17.7% to 113.1%, SD = 21.8%), which was significantly greater than the mean increase of children at GMFCS levels I and II (P = 0.044 and P = 0.031, respectively). However, not all children who were able to increase their gait speed

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Time-Distance Parameters	GMFCS I	GMFCS II	GMFCS III	TD
No. subjects fast/free (%)	77/80 (96)	90/91 (99)	14/41 (34)	34/34 (100
Velocity (SD) (m/s)*				
Free speed	1.03 (0.17)	0.95 (0.17)	0.72 (0.23)	1.21 (0.22)
Fast speed	1.46 (0.25)	1.35 (0.22)	1.19 (0.21)	1.83 (0.25)
Stride length (SD) (m)*				· · · · ·
Free speed	1.05 (0.13)	0.94 (0.15)	0.82 (0.19)	1.16 (0.18)
Fast speed	1.23 (0.15)	1.09 (0.18)	1.05 (0.19)	1.37 (0.22)
Cadence (SD) (steps/min)*				· · · · ·
Free speed	117 (12.0)	122 (16.1)	104 (29.6)	125 (15.8)
Fast speed	143 (18.5)	151 (18.8)	139 (21.4)	163 (20.9)

TABLE 2 Means and SDs of TDD Among	TD and GMFCS Levels at Free and Fast Speeds
TABLE 2. Means and SDS OF TDP Among	TD and Giving's Levels at free and fast speeds

increased their stride length greater than MCID. Therefore, mean increase in stride length for children at GMFCS I was 18.3% (6.25% to 41.9%, SD = 8.2%), at GMFCS II was 17.6% (4.7% to 39.4%, SD = 8%), and at GMFCS III was 16% (6% to 30.3%, SD = 7.4%). Children in the TD group had a mean increase in stride length of 18% (4.8% to 46.1%, SD = 10.3%). There were no significant differences among the TD group or GMFCS levels for mean increase in stride length. Similarly, not all children who were able to increase their gait speed increased their cadence greater than MCID. Mean increase in cadence for children at GMFCS I was 23% (6.6% to 49.7%, SD = 10.4%), at GMFCS II was 26% (8% to 58.4%, SD = 9.5%), and at GMFCS III was 29% (8.7% to 60.5%, SD = 16.8%). Children in the TD group had a mean increase in cadence of 30% (8.5% to

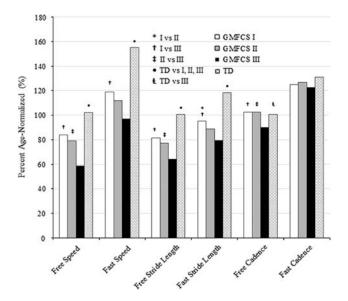


FIGURE 2. Histogram comparing percent means (normalized to age) of time-distance parameters by typically developing (TD) and Gross Motor Function Classification System (GMFCS) levels at free and fast walking speeds. Statistical differences between groups are listed. *I versus II, †I versus III, ‡II versus III, •TD versus I, II, III, \Box TD versus III, P < 0.05.

56.2%, SD = 13.1%), which was significantly greater than that of children at GMFCS level I (P = 0.005).

DISCUSSION

The ability to control gait speed is important for a wide range of functional and social activities. The consistent mechanisms for increasing gait speed utilized by TD children presumably reflect an underlying drive to maximize energy efficiency across the range of gait speeds required in daily life.⁴⁻⁸ Previous studies suggest that while the ability to increase gait speed is common in children with CP, the mechanisms by which they control gait velocity are distinct relative to TD peers, due to spasticity, impaired selective voluntary motor control, disrupted body position sense, and the presence of muscle contractures and skeletal malalignments.²⁵⁻³⁰ Control of stride length is thought to be more affected than control of cadence in children with CP.^{12,31} For these children, increased velocity is thought to be achieved primarily by increasing cadence, which is presumably less energy efficient than mechanisms that include control of stride length as well.

The current study assessed and compared the ability of children with CP, segregated by GMFCS level, to voluntarily increase the speed of their gait above the MCID, with another cohort of TD children. There were statistically significant age differences between several of the groups. Mature kinematic gait patterns are achieved by 7 years of age in TD children.⁶ Improvements in motor function (as measured by the gross motor function measure) related to growth and development in children with CP, across GMFCS levels, also plateau by around 7 years of age.²³ These differences in age between the CP children, as an entire group and when segregated by GMFCS, and the TD children are between 10 and 14 years of age, which is well above the age level where age-related changes would be present. So, although the age differences noted above are statistically significant, they are not clinically significant relative to the data analyzed in the current study.

The hypothesis that most ambulatory children with CP can increase their gait velocity, based upon the clinical impression that the ability to control gait speed is "common" in children with CP who are ambulatory, is

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Time-Distance Parameters	GMFCS I	GMFCS II	GMFCS III	TD	P †	Group Differences‡ (P)
No. subjects (fast/free)	77/80	90/91	14/41	34/34		
Velocity (SD) (m/s)*						
Free speed	83.4% (14.3%)	79% (14.6%)	58.7% (19.1%)	102.3% (19.6%)	< 0.001	I, II vs. III (< 0.001); TD vs. I, II, III (< 0.001)
Fast speed	118.9% (21%)	112% (18%)	97.3% (17.5%)	155.1% (21%)	< 0.001	I vs. III (< 0.001); TD vs. I, II, III (< 0.001)
Stride length (SD) (m)*						
Free speed	81.6% (11%)	77.1% (11.5%)	64.2% (13.9%)	100.7% (13.7%)	< 0.001	I, II vs. III (< 0.001); TD vs. I, II, III (< 0.001)
Fast speed	95.2% (12.1%)	88.7% (12.1%)		118.5% (13.8%)		I vs. II (0.005), I vs. III (< 0.001);
1	· · · · ·	,	· · · · · ·			TD vs. I, II, III (< 0.001)
Cadence (SD) (steps/min)*						
Free speed	102.5% (9.2%)	102.6% (11.2%)	90.1% (25.2%)	100.9% (8.9%)	< 0.001	I, II vs. III (< 0.001); TD vs. III (0.006)
Fast speed	125% (13.4%)	()	()	131.3% (15.5%)	0.099	

TABLE 3. Percent of Age-Normalized Means and SDs of TDP Among TD and GMFCS Levels at Free and Fast Speeds

*Values are reported as mean and SD.

†P-value is the significance of the F ratio for the analysis of variance between groups.

‡Group differences indicate results of post hoc Bonferroni comparison.

GMFCS indicates Gross Motor Function Classification System; NS, not significant; (fast/free), fast speed/free speed; TD, typically developing; TDP, time-distance parameter.

supported by the data from this study. However, more precise analysis is possible when the children are evaluated based upon motor impairment level as reflected by the GMFCS. Almost all children at the highest functional levels (ie, GMFCS I and II, 96% and 99%, respectively) were able to control their gait speed. Almost all of the subjects with hemiplegic and diplegic CP functioning at the GMFCS I and II levels were able to voluntarily increase gait speed, suggesting that CP hemiplegics and diplegics at GMFCS I and II levels have similar speed control ability. The imprecision of the topographic classification scheme for CP (even between hemiplegic and diplegic types) limits our confidence in further analysis of these data. Interestingly, only a third (34%) of children at the GMFCS III level were able to control gait speed. At

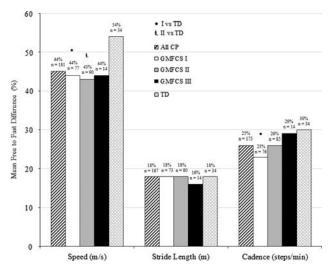


FIGURE 3. Histogram comparing percentage of change in time-distance parameters, shown above along with number of subjects, as the study groups [Gross Motor Function Classification System (GMFCS) I, II, II, all cerebral palsy, and typically developing (TD)] increase speed. Statistical differences between groups are listed. •I versus TD, \Box II versus TD, P < 0.05.

the GMFCS III level, the majority of children had no previous surgery, and the number with previous surgery (typically 2 years or more from the index gait study) was small, limiting our ability to perform further analysis concerning the consequence of temporally distal surgery on the ability to voluntarily increase gait speed. Clinicians recognize the GMFCS III level to be transitional with respect to natural history of ambulation, with deterioration of motor function (as measured by the gross motor function measure) over time.³² In addition, the outcomes following SEMLS interventions are variable, with dramatic improvements achieved in certain children at the GMFCS III level and progressive deterioration despite aggressive surgery and rehabilitation noted in others.^{14–21,33} Although clinicians have presumed that the ability to control gait speed is a positive predictor of a better outcome following SEMLS in children at the GMFCS III level, there is no study supporting or validating this concept. This study suggests that children at the GMFCS III level can be divided into 2 groups based upon their ability to control gait velocity, (eg, IIIa: able to increase gait speed and IIIb: not able to increase gait speed), though further study relating this ability to outcomes following SEMLS remains to be done. Previous work from our center has quantified the concept of a strength-to-weight ratio, and identified a level below which independent ambulation is not likely.³³ The ability to prognostically subdivide children at the GMFCS III level based upon a matrix of such variables (eg, control of gait velocity, strength, and weight) has the potential to enhance clinical decision making for interventions such as surgery, rehabilitation, orthoses, and assistive devices.

The data from this study partially support the hypothesis that the TDPs at free and fast walking speeds are related to the degree of motor impairment as reflected by GMFCS levels. At free speed, which was self-selected, speed, stride length, and cadence all discriminated between those children who walked independently (GMFCS I and II) and those who did not (GMFCS III). However, none of the parameters discriminated between the higher

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functional levels of GMFCS I and II. At fast speed, a high demand situation, stride length was the best discriminator among GMFCS levels (I vs. II, II vs. III), and cadence was the worst discriminator, with no differences among GMFCS levels. It should be noted that only a subset of the GMFCS III subjects (ie, those able to increase velocity above MCID, the previously described IIIa group, 14 of 41 children), were included in this level of the analysis. Their TDP profiles appear to be more similar to the GMFCS I and II groups than the IIIb subgroup (ie, those not able to increase gait speed), suggesting a less severe impairment level for the IIIA subgroup, which may be a prognostic variable for outcomes following a variety of interventions to improve gait.

The data from this study do not support the hypothesis that strategies used to increase gait speed are distinct among GMFCS levels. Children in the TD group exhibited significantly greater speed and stride length than all of the subjects in the CP group, at both free and fast speeds, regardless of GMFCS level. Cadence was a poor discriminator between TD and CP groups at both free and fast speeds. The TD group showed a significantly greater percent increase in velocity from free to fast speed trials than the CP group, regardless of GMFCS level. However, there was only 1 significant difference in percent change in stride length and cadence for free to fast walking between TD and CP groups, regardless of GMFCS level (change in cadence between TD and GMFCS I).

There were no significant differences in the percent change in TDPs (velocity, stride length, or cadence) from free to fast walking among GMFCS levels. The mean increase in velocity (54%) for the TD group was achieved by increases in both stride length (18%) and cadence (30%). The mean increase in velocity (44%) for the CP group was achieved by increases in both stride length (18%) and cadence (25%). This suggests the presence of consistent underlying pathophysiologic processes in children with CP who are ambulatory, regardless of functional impairment as measured by the GMFCS. The difference in results for this topic relative to the previous study by Abel and Damiano may be explained by the current study's more robust study design. The current study has a much larger sample size (212 vs. 24 children with CP in the Abel and Damiano study), improved classification of subjects (GMFCS vs. community/limited community ambulators in the Abel and Damiano study), and more precise calculation and definition of significant changes in gait velocity (MCID vs. any measured increase in the Abel and Damiano study).¹² Further study is required to better understand the relative mechanisms utilized to control gait velocity in children with CP.

In summary, almost all children with CP at the GMFCS I and II levels can control the speed of their gait, whereas only a third at the GMFCS III level have the ability to do so. The clinical significance of this remains to be determined. Stride length is the most discriminatory (and cadence the least) TDP measure among GMFCS levels for both free and fast walking. The mechanisms by which

children with CP increase gait velocity (ie, utilization of changes in stride length and cadence) are comparable across GMFCS levels, suggesting the presence of consistent underlying pathophysiologic processes.

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