Fatigue in Children with Perinatal Stroke: Clinical and Neurophysiological Associations

Wrightson. J.G [1], Zewdie, E.[2,3,4,5]. Kuo, H.-C. [2,3,4,5]. Millet, G.Y [1,6]. and Kirton, A. [2,3,4,5].

1. Human Performance Laboratory, University of Calgary, Calgary, AB, Canada
2. Calgary Pediatric Stroke Program, Alberta Children's Hospital, Calgary, AB, Canada
3. Alberta Children's Hospital Research Institute (ACHRI), Calgary, AB, Canada
4. Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada
5. Department of Pediatrics and Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary AB, Canada
6. Univ Lyon, UJM-Saint-Etienne, Inter-university Laboratory of Human Movement Biology, EA 7424, F-42023, Saint-Etienne, France.

Corresponding Author: Adam Kirton, Department of Pediatrics and Clinical Neurosciences, Cumming School of Medicine, University of Calgary, 2888 Shaganappi Trail NW, Calgary, Alberta, T3B 6A8, Canada.
Email: adam.kirton@ahs.ca
OCRID: 0000-0001-5209-3374

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Abstract

Aim

We aimed to characterize fatigue in hemiparetic children with perinatal stroke and explore associations with measures of motor performance and corticospinal excitability.

Method

Forty-five children, aged 6-18 years, with magnetic resonance imaging confirmed perinatal stroke participated. Associations between fatigue (Pediatric Quality of Life Inventory V3.0 cerebral palsy module (PEDSQL-CP) fatigue subscale), motor performance (Assisting Hand Assessment, Box and Blocks test, grip strength) and excitability of corticospinal projections to both hands were examined using ranked tests of correlation, robust regression and the Mann-Whitney U test.

Results

Nearly half of participants (47%) reported experiencing fatigue in the previous month. Function in the less-affected hand (Box and Blocks, grip strength) was correlated with fatigue scores. Participants with preserved ipsilateral projections to the more affected hand had less fatigue, and scores correlated with the excitability of these projections. Fatigue scores were not associated with age, gender, or AHA.

Interpretation

Fatigue is common in hemiparetic children with perinatal stroke and is associated with motor performance and the presence and excitability of ipsilateral corticospinal projections from the contralesional hemisphere to the more affected hand.

Abbreviations

CP
Cerebral palsy

PEDSQL-CP
Pediatric Quality of Life Inventory V3.0 cerebral palsy module

TMS
Transcranial Magnetic Stimulation

MEP
Motor Evoked Potential

FDI
First Dorsal Interosseous

EMG
Electromyography

RMT
Resting Motor Threshold

Perinatal stroke is the predominant cause of unilateral cerebral palsy (CP) and usually results in lifelong disability[1]. Fatigue is a frequently reported debilitating symptom in children with CP which can reduce quality of life, independence and mobility[2]. To date, no studies have examined the factors associated with fatigue in children with perinatal stroke. Despite its prevalence, the causes of fatigue in children with perinatal stroke and unilateral cerebral palsy are unknown, and there are no therapies that target fatigue in these children[2].

Fatigue is a sensation of tiredness, often accompanied by alterations in behaviour or performance, which can arise from sustained performance in a mentally or physically demanding task, or can be chronic and often unrelated to activity[3,4]. Fatigue is a symptom of many neurological diseases, and can be caused by a number of underlying physiological and psychological mechanisms [4,5]. Whilst the causes of fatigue in children with perinatal stroke are unclear, in adults with stroke several factors have been associated with fatigue severity including reduced muscle strength, pain, and impaired motor control and manual dexterity [6–9]. Although there are descriptive reports linking fatigue with problems with motor control and weakness in children with CP[10,11] to date there has been no examination of whether fatigue severity is associated with these factors in children with perinatal stroke.

Fatigue is also suggested to arise, in part, from dysfunction in an excitation-facilitation corticospinal output system[12] and reduced corticospinal excitability has been associated with fatigue in adults with chronic fatigue syndrome[13], multiple sclerosis[14] and stroke[15]. The relationship between corticospinal excitability, motor performance and fatigue is not well understood, but it is possible that reduced corticospinal excitability after stroke may either cause, or be the result of, a mismatch between the predicted and actual sensory consequences of descending motor commands[16]. Unilateral injury to the corticospinal system often leads to atypical development of the corticospinal tract[17]. The ipsilateral projections from the motor cortex present at birth are usually pruned in early development but are often preserved in hemiplegic cerebral palsy[17–19]. The presence of an ipsilateral evoked response during transcranial magnetic stimulation (TMS) of the contralesional hemisphere is associated with poorer performance tests of manual dexterity in children with perinatal stroke[20,21]. The excitability of corticospinal projections also appears to be related to motor performance in children with perinatal stroke[21].

There is growing evidence that identifying the causes and potential treatments for fatigue in children with CP should be a focus for rehabilitation[10]. Whether fatigue in children with perinatal stroke is associated with strength, motor performance and corticospinal excitability has not been examined. The aim of this study was to explore the associations between fatigue and measures of muscle strength, motor performance, pain and corticospinal excitability in children with perinatal stroke. We hypothesized that high levels of fatigue would be associated with lower levels of strength, motor performance and corticospinal excitability. Because corticospinal excitability and corticospinal tract organization in both hemispheres is associated with motor performance in children with perinatal stroke[21], we also hypothesized that the presence and excitability of ipsilateral projections from the contralesional hemisphere would be associated with higher levels of fatigue.

Method

Participants

Participants were recruited via a population-based research cohort, the Alberta Perinatal Stroke Project and were enrolled in the PLASTIC CHAMPS clinical trial of repetitive TMS and constraint therapy in children with perinatal stroke[22]. Inclusion criteria were: age 6-19 years; term birth; magnetic resonance imaging (MRI)-confirmed unilateral perinatal arterial ischemic stroke or periventricular venous infarction, symptomatic hemiparetic cerebral palsy including Pediatric Stroke Outcome Measure >0.5; Manual Ability Classification Scale (MACS) levels I-IV; both parent and child perceived functional limitations; written informed consent and/or assent. Exclusion criteria were multifocal stroke, additional neurological abnormality, severe hemiparesis (MACS V) or predominant dystonia, unstable epilepsy, contraindications to TMS, or upper extremity surgery or botulinum toxin within the 12 months prior to testing. Experiments were carried out with the approval of the Research Ethics Board at the University of Calgary.

Experimental protocol

Within the above trial, all participants underwent a standardized protocol that included detailed measures of quality of life, motor function, and TMS measures of motor cortex neurophysiology. Following clinical assessment of manual motor performance, participants attended the Alberta Children's Hospital Pediatric Non-Invasive Brain Stimulation Laboratory.

Fatigue and quality of life measures

Self-reported fatigue and quality of life were assessed with the Pediatric Quality of Life Inventory (PEDSQL) 3.0 cerebral palsy (CP) module, a validated measure of quality of life in children with CP[23]. The fatigue subscale consists of four statements/categories with the child asked to rate how often they have experienced each in the month prior to assessment: "I feel tired", "I feel physically weak (not strong)", "I rest a lot" and "I don't have enough energy to do things that I like to do". Children were asked to give a rating of 0-4 for each statement if they never (0), almost never (1), sometimes (2), often (3), or almost always (4) experienced the problem. Children were classified as experiencing fatigue if they scored at least 2 ("sometimes" a problem) on two or more of the categories of fatigue, or if they scored 4 ("almost always" a problem) for one of the categories (a PESQL-CP Fatigue score $\leq$68.75). For children under 8 years, parents assisted with the rating using the PEDSQL 3.0 CP module parent report for young children. The PEDSQL scores for Fatigue, were reverse scored and linearly transformed to a 0 to 100 scale. The average score across all categories in each subscale was calculated. Lower scores in each subscale represent higher levels of fatigue[23].

Strength and motor performance measures

Motor performance was assessed using two validated measures of bimanual and unimanual dexterity in children with CP: The Assisting Hand Assessment (AHA) and the Box and Blocks test. The AHA measures how well children with unilateral upper limb impairment utilize their more affected hand in bimanual activities and is a valid and reliable measure of upper limb function in children with hemiparesis[24]. The adolescent version of the AHA was used in children over 12 years old. Assessments were videotaped for validation and scoring. Scores are expressed in AHA logit units (maximum 100). The Box and Blocks test is a validated test of unimanual function which measures the speed of lifting, carrying and releasing blocks in a 60s period. The number of blocks moved in the 60s period was recorded for each hand. Grip strength, a measure of hand power quantified in kilograms of force, was measured using a hand dynamometer over three trials separated by 15s of rest, and the highest force generated was recorded. Motor assessments were administered by blinded, experienced, certified pediatric occupational therapists.

Corticospinal arrangement and excitability measures

TMS was used to assess corticospinal excitability of each hemisphere. Data were collected as part of a larger project examining corticospinal arrangement and excitability in children with perinatal stroke[25]. Motor evoked potentials (MEP) were measured from the first dorsal interosseous (FDI) muscle with single-pulse TMS, using a figure-of-eight coil (70 mm) connected to a Magstim Bistim2 stimulator (Magstim; Dyfed, UK). The coil was tangentially angled at 45 degrees to induce posterior-anterior currents in the motor cortex. MEP were recorded using surface electromyography (EMG) via a pair of Ag-AgCl electrodes on both FDI (Kendall; Chicopee, MA, USA, 1.5-cm radius). EMG signals were amplified (x1000), band-pass filtered (20-2000 Hz) and digitized (5000 Hz) using CED 1401 hardware and Signal 6.0 software (Cambridge Electronic Design, Cambridge, UK). All stimulations were performed in the relaxed muscle. EMG data were exported to MATLAB (Mathworks, Inc., Natick, MA) for blinded offline analysis. Stimulation data were visually inspected for artifacts and customized scripts were used to calculate peak-to-peak MEP amplitudes from un-rectified EMG (time window from stimulation artifact of 15-60 ms).

The location over the primary motor cortex in each hemisphere that produced the largest contralateral MEP was identified as TMS 'hotspot' and was marked on a 3-dimensional anatomical T1 MRI using neuro-navigation (Brainsight 2, Rogue Research, Montreal, Canada). These hotspots were used for all subsequent stimulations. In the stroke hemisphere, the border of cortical lesions was explored to elucidate any obtainable ipsilesional TMS responses. Resting motor threshold (RMT) was then defined as the minimum percentage of maximum stimulator output (%MSO) required to elicit MEP with peak-to-peak amplitude of > 50μV in 5 of 10 consecutive trials. RMT was determined for both the ipsilesional and contralesional hemispheres. The peak-to-peak amplitude of the FDI MEP (mV) of both hemispheres was measured in both the affected and less-affected hands. MEP amplitude was measured in the less affected hand during TMS of the contralesional hemisphere. Due to the common presence of ipsilateral projections to the more affected hand from the contralesional hemisphere[21], MEP amplitude was measured in the affected hand during TMS of both hemispheres. The MEP amplitude for the less affected hand was measured using TMS at 120% of the contralesional motor threshold. Because contralesional motor thresholds for the affected hand may be higher than those for the less-affected hand[20], MEP amplitude was measured using TMS at both 120% and 130% of contralesional motor threshold.

The presence of ipsilateral projections from the contralesional hemisphere to the affected hand was dichotomized as present or absent using previously published methods[25]. Participants were classified as having ipsilateral projections if contralesional TMS at 120% of the of contralesional motor threshold resulted in a MEP with a peak-to peak amplitude >50 μV in the affected hand in at least 3 out of 10 trials. Otherwise they were classified as having contralateral only projections.

Statistical Analysis

Data were analysed for normality using Q-Q plots and the Shapiro-Wilks tests of normality. Because data for the fatigue PEDSQL-CP sub-scale violated assumptions of normality and distribution required for standard parametric tests, the Spearman's test of rank-order correlations (*rho*) was used to examine the associations between fatigue scores and age, grip strength, motor performance and corticospinal excitability. Multiple comparisons were controlled for using the false discovery rate[26]. The effect of gender, stroke type and corticospinal tract arrangement on fatigue scores was examined using the Mann-Whitney U test (U), with *r* used as an estimate of the effect size (*r*). Robust linear regression was used to determine variance in fatigue explained by measures of motor performance and corticospinal excitability, the standardised beta coefficient (β) its associated 95% confidence interval (95%CI) and standard error (SE), plus the coefficient of determination (R^2) are reported. Statistical procedures were performed in R, version 3.4.3.

Results

All forty-five participants completed all assessments. Median age was 11 years, range 6-19 years, 64% male. Participant demographics and outcomes are summarized in Table 1. Forty-seven percent (21/45) of the children reported experiencing fatigue (PESQL-CP fatigue score $\leq$68.75). Fatigue scores were not associated with age or stroke type and did not differ between males and females ($p > 0.05$).

Table 1. Here Please

Fatigue and motor performance

The PEDSQL-CP fatigue score correlated with grip strength in the less affected (*rho* = 0.38, p = 0.015) but not more affected (*rho* = 0.28, p = 0.058) hand. Those with higher fatigue (a low PEDSQL score) had lower grip strength in the less affected hand (Figure 1A). Fatigue scores were correlated with Box and Blocks performance in the less affected (*rho* = 0.42, p = 0.009) but not the more affected hand (*rho* = 0.20, p = 0.122). Those with higher fatigue (lower PEDSQL scores) had poorer performance on the box and blocks test for the less affected hand (Figure 1B). Fatigue scores did not correlate with AHA performance (*rho* = 0.02, p = 0.304).

Figure 1. Here Please

Fatigue and corticospinal excitability

As responses in the more affected hand were only evoked by TMS of the ipsilesional hemisphere in 7 participants, this data could not be modelled and was excluded from further analysis. Evoked responses following TMS in the contralesional hemisphere were available in a subset of children. For the more affected hand, 20 participants had response at 120% of resting motor threshold (RMT) and 22 had responses at 130% resting motor threshold. Because data were collected in a paradigm examining the corticospinal excitability in a range of thresholds above RMT (100-150%)[25], participants were excluded if 150% RMT was over 100% of maximum stimulator output. In the less affected hand, 25 participants had measurable responses. Mean contralesional

RMT was 58$\pm$18% maximum stimulator output while mean ipsilesional RMT was 68$\pm$18% (p < 0.001).

Fatigue scores were higher (indicating lower fatigue) in the ipsilateral group compared to those without prominent ipsilateral projections (U = 64.5, p = 0.035, r = -0.33, Figure 2A). Fatigue scores were positively correlated with MEP amplitude in the more affected hand at both 120% RMT (*rho* = 0.45, p = 0.048) and 130% RMT (*rho* = 0.57, p = 0.013, Figure 2B), where those with lower fatigue (higher PEDSQL fatigue scores) had increased corticospinal excitability of projections to their affected hand. Fatigue scores were not correlated with MEP amplitude in the less affected hand (*rho* = 0.37, p = 0.058) or with contralesional RMT (*rho* = -0.24, p = 0.109).

To examine the variance in fatigue explained by both motor performance and corticospinal excitability, robust linear regression was performed with Box and Blocks performance in the less affected hand and corticospinal excitability of the ipsilateral projections as the predictors, and fatigue scores as the dependent variable. Univariate linear regression revealed that both Box and Blocks performance (β = 0.73, 95%CI [0.38-1.09], SE = 0.17, multiple R^2 = 0.26) and corticospinal excitability (β = 11.3, 95%CI[4.91-19.34], SE = 3.2, multiple R^2 = 0.22), were significant predictors of the variance in fatigue. A multivariate model containing both predictors significantly increased the explained variance in fatigue scores (p = 0.004, R^2 = 0.36).

Figure 2. Here Please

Discussion

The aim of the present study was to examine the relationship between fatigue, motor performance and corticospinal excitability in hemiparetic children with perinatal stroke. Approximately half (47%) of participants reported experiencing fatigue. Fatigue scores were correlated with motor performance and grip strength in the less affected hand. Contrary to our hypothesis, children with preserved ipsilateral projections from the contralesional hemisphere to the more affected hand had *less* fatigue than those with contralateral projections. Fatigue scores were also correlated the excitability of the ipsilateral corticospinal projections and were associated with self-reported pain and problems with movement and balance. This study is the first to show that fatigue in hemiparetic children with perinatal stroke is associated with motor performance and clinical neurophysiology.

The present study is the first to examine the correlates of fatigue in children with hemiparetic perinatal stroke. Almost half of the children reported experiencing fatigue in the previous month. Whilst the causes of fatigue in perinatal stroke are unknown, in adults with stroke both muscle strength[8] and motor performance[6,9] have been associated with fatigue. Here we extend these findings to show that both grip strength and motor performance in the Box and Blocks test were associated with fatigue in children with perinatal stroke.

However, in contrast to our predictions and previous data in adults with stroke[9], the association between fatigue and motor performance was only present in the less affected hand. Children with unilateral CP typically favour their less affected hand, especially when performing bimanual tasks[24]. Improving performance in the more affected hand is frequently the primary focus of rehabilitation[27]. However, there is increasing evidence that compared to typically developed children, performance in the less affected hand is also impaired in unilateral CP and perinatal stroke specifically[20]. Our study is the first to show that differences in motor performance in the less affected hand are associated with fatigue. The mechanisms which underpin this relationship are unclear, however, recent predictive coding accounts posit that fatigue arises from the discrepancies between the predicted sensory consequences of a motor command, and the afferent sensory information which results from motor action[28]. Because children with unilateral CP favour their less affected hand, it follows that the sensory consequences of movement and performance in this hand may be the most likely to be those perceived and interpreted by the child. Detailed robotic assessments have recently quantified the common occurrence of complex sensory dysfunction in children with perinatal stroke[29,30]. The current data further strengthen recent calls for more research examining the effects of rehabilitation of the less affected hand on function in children with perinatal stroke[31], and suggest that the effect of rehabilitation of the less affected hand on fatigue should also be examined.

Fatigue was associated with the presence and excitability of ipsilateral projections from the contralesional hemisphere to the more affected hand. Early insult to the corticomotor system leads to atypical developmental organization of the central nervous system, including the corticospinal tracts[17]. In children with hemiparesis, ipsilateral projections from the contralesional hemisphere to the more affected hand, typically pruned during development, can be preserved[18]. When identified using TMS to evoke responses in the more affected hand, these projections have often been associated with poorer motor performance[20,21]. The presence of these ipsilateral projections have previously been considered the consequence of maladaptive plastic development of the corticospinal system[20]. However, many exceptions to this general concept are recognized. The present data suggests that the presence and strength of ipsilateral pathways is associated with lower levels of fatigue and results from the robust linear regression indicate that in children with preserved ipsilateral projections, both the excitability of these projections and motor performance of the less-affected hand combined account for a greater proportion of variance in fatigue than either predictor in isolation. This is a surprising result given the frequent association between ipsilateral projections and poorer motor performance. These data suggest that measures of motor performance and fatigue may be representing different functional constructs in this population. The MEP may be considered to reflect the relative integrity of descending corticospinal projections[32]. Although no causal relationship can be inferred from the present data, our results may indicate that fatigue in children with hemiparetic perinatal stroke is associated with the integrity of descending projections from the contralesional hemisphere. Kuppuswamy et al[16] have suggested that post-stroke fatigue in adults arises from a mismatch between the efferent and afferent sensory information processed by the sensorimotor system. It is possible that in children with perinatal stroke, the presence of these ipsilateral projections somehow alters precision of the sensory predictions encoded by the corticospinal system[33]. Alternatively, disruptions in sensorimotor processing have previously been identified in people with CP who have preserved ipsilateral projections[34]. Although speculative, it is possible that the presence of these projections may alter sensation of fatigue via disruption in sensory processing during motor performance. Examination of the associations between functional brain activity, corticospinal excitability, motor performance and fatigue in children with perinatal stroke is warranted to improve understanding of the nature and direction of the sensory information which may contribute to fatigue in this population.

The regression model with corticospinal excitability and box and blocks performance explained 36% of the variance in fatigue scores. Whilst a great deal of the variance in fatigue remains unexplained, this finding suggests that both of these factors could be future targets for therapies. It has been suggested that treatments which alter corticospinal excitability could be a method to alleviate fatigue in adult stroke[16]. Non-invasive brain stimulation techniques which modulate corticospinal excitability have been shown to be well tolerated in children with perinatal stroke[35]. The impact of these techniques on fatigue should be a topic for future research. Rehabilitation programs for children with unilateral cerebral palsy typically investigate the performance, and control of, the more affected limbs. The present data suggest that control of the less affected hand is at least as important for quality of life and fatigue in children with hemiparetic perinatal stroke. Further research is required to investigate whether interventions which result in neuroplastic and performance adaptions in the less affected limbs can reduce fatigue in these children. Whether measures of change in fatigue should also be employed as a potential outcome within interventional trials requires additional consideration.

Limitations include our measure of fatigue as the PEDSQL-CP is well validated but only consists of a few questions and may miss some of the more subtle details of fatigue in children with CP. There have been recent advances in the measurement of fatigue in CP[2,10], and future research may benefit from using more comprehensive tools such as the Fatigue Impact and Severity Self Assessment (FISSA[10]). The present study only measured associations with trait (chronic) fatigue, but not the associations between state fatigue, motor outcomes and corticospinal excitability. The interactions between these factors should be investigated in future studies. Our sample was carefully selected for a clinical trial with rigorous criteria, and this may limit generalizability to larger populations of children with perinatal stroke. Our TMS methods were relatively simple: We did not normalize MEP to the muscle compound action potential ("Mmax") to account for changes in peripheral signal conduction, and more complex interrogations of cortical neurophysiology with this and other advanced neurotechnologies may further inform the relationship between fatigue, motor performance and corticospinal neurophysiology in children with perinatal stroke.

Conclusions

Fatigue is common in hemiparetic children with perinatal stroke and associated with motor performance in the less affected hand. The presence and excitability of ipsilateral projections from the contralesional hemisphere to the more affected hand are associated with lower levels of fatigue. Future studies are required to better define the mechanisms of fatigue after perinatal stroke and its potential as a target to improve outcomes for affected children.

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Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Figures

Figure 1. Fatigue and motor performance in children with perinatal stroke (N = 45) . (A) Correlation between PEDSQL-CP fatigue score and grip strength in the less affected hand. (B) Correlation between PEDSQL-CP fatigue score and Box and Blocks performance in the less affected hand. Those with higher fatigue had lower grip strength and poorer box and blocks performance in the less affected hand.

Figure 2. TMS neurophysiology and fatigue . (A) PEDSQL fatigue score in the contralateral (N = 11) and ipsilateral groups (N = 22), bars represent median +IQR. (B) Correlation between PEDSQL fatigue score and peak to peak MEP amplitude (mV) in the more affected hand (n = 22), evoked by TMS of the contralesional hemisphere at 130% of motor threshold.

Table

Table 1. Demographics characteristics, quality of life and clinical measures

	All Participants (n = 45)
Gender (Female: Male)	16 (36%):29(64%)
Age (Years mean±SD)	12±4
Stroke side (Left: Right)	25(56%):20(44%)
Stroke type (Arterial: Periventricular Infarction)	29(64%):16(36%)
Fatigue (PEDSQL, median [IQR])	75.0 (62.5-87.5)
Pain and Hurt (PEDSQL, median [IQR])	81.3 (62.5-87.5)
Movement and Balance (PEDSQL, median [IQR])	85.0 (75.0-95.0)
Grip Strength, less affected hand (KG, mean±SD)	17.7 ± 9.7
Grip Strength, more affected hand (KG, mean±SD)	7.3 ± 5.8
AHA (Logit units, mean±SD)	60.9 ± 20.3
Box and Blocks, less affected hand (Number of blocks, mean±SD)	47.4 ± 13.2
Box and Blocks, more affected hand (Number of blocks, mean±SD)	21.9 ± 14.7