ORIGINAL ARTICLE

Quality of Life, Cognition and Mood in Adults with Pediatric Multiple Sclerosis

Kristen M. Krysko, Paul O'Connor

ABSTRACT: ***Background:*** Pediatric onset multiple sclerosis (MS) negatively affects cognitive function, mood and health related quality of life (HRQOL). We aimed to explore the cognitive, psychological and HRQOL impacts of pediatric MS on young adults and to explore the relationships between disability, disease duration, cognition, mood and HRQOL in this hypotheses generating study. ***Methods:*** Thirty-four young adults with pediatric onset MS at St. Michael's Hospital in Toronto were included in this cross-sectional study (mean age 21.3 years, 56% female). Participants completed assessments of physical disability (Expanded Disability Status Scale (EDSS)), cognitive function (Symbol Digit Modalities Test (SDMT)), mood (Beck Depression Inventory II (BDI-II)), and HRQOL (Short Form Health Survey (SF-36v2)). Findings were compared to age- and gender- matched normative data. ***Results:*** Individuals with pediatric MS performed worse on the SDMT compared to normative data, with 53% demonstrating cognitive impairment. There was no difference in BDI-II scores from normative data, but 21% showed at least mild depression. There was a non-significant impairment in physical HRQOL compared to normative data. Decreased physical HRQOL was related to disability (EDSS), while mental HRQOL was related to depression (BDI-II). ***Conclusions:*** Young adults with pediatric MS have reduced cognitive function. Non-significant reductions in HRQOL may be partly attributed to physical disability and depression. These factors should be addressed in the care of adults with pediatric MS. Further studies including control groups and longitudinal design are needed to confirm these findings.

RÉSUMÉ: Qualité de vie, cognition et humeur chez des adultes atteints de sclérose en plaques pédiatrique. ***Contexte:*** Le début de la sclérose en plaques (SP) à l'âge pédiatrique a des effets négatifs sur la fonction cognitive, l'humeur et la qualité de vie liée à la santé (QVLS). Le but de cette étude de génération d'hypothèses était d'explorer les impacts cognitifs, psychologiques ainsi que sur la QVLS de la SP pédiatrique chez de jeunes adultes et d'examiner les relations entre l'invalidité, la durée de la maladie, la cognition, l'humeur et la QVLS. ***Méthode:*** Trente-quatre jeunes adultes atteints de sclérose en plaques ayant débuté avant l'âge adulte, suivis à l'Hôpital St. Michael's de Toronto, ont été inclus dans cette étude transversale (âge moyen des patients : 21,3 ans, dont 56% étaient de sexe féminin). Les participants ont complété des évaluations de l'invalidité physique (Échelle étendue du statut d'invalidité (EDSS)), des fonctions cognitives (Symbol Digit Modalities Test (SDMT)), de l'humeur (Inventaire de dépression de Beck II (BDI-II)) et la QVLS (Short Form Health Survey (SF-36v2)). Les données recueillies chez les patients ont été comparées à des données normatives appariées pour l'âge et le sexe. ***Résultats:*** Les patients atteints de SP pédiatrique avaient des scores moins bons au SDMT par rapport aux données normatives, 53% présentant une altération cognitive. Il n'existait pas de différence dans les scores au BDI-II par rapport aux données normatives, mais 21% présentaient au moins une légère dépression. Il existait une altération non significative de la QVLS physique par rapport aux données normatives. La diminution de la QVLS physique était en lien à l'invalidité (EDSS), alors que la QVLS mentale était liée à la dépression (BDI-II). ***Conclusions:*** Les jeunes adultes atteints de SP pédiatrique ont une fonction cognitive altérée. Des diminutions non significatives de la QVLS peuvent être attribuées partiellement à l'invalidité physique ainsi qu'à la dépression. Ces facteurs devraient être pris en compte dans le contexte de soins prodigués aux adultes atteints de SP pédiatrique. De nouvelles études incluant des groupes témoins et un plan d'étude longitudinal sont nécessaires afin de confirmer ces observations.

Keywords: Cognition, depression, mood, multiple sclerosis, pediatrics, quality of life

doi:10.1017/cjn.2015.354 Can J Neurol Sci. 2016; 43: 368-374

Multiple sclerosis (MS) is a demyelinating and neurodegenerative disease of the central nervous system (CNS). Onset is typically in early adulthood, but three to five percent of cases begin in childhood.[1,2] The course of pediatric MS tends to involve a higher relapse rate compared to adult onset disease,[3] but typically involves less severe neurologic impairment with a longer duration to reach severe disability.[4] In addition to physical neurologic impairment, there is associated cognitive impairment, depression and fatigue, which may negatively impact health related quality of life (HRQOL) as in adult onset MS.

Over the last several years, it has been demonstrated that during childhood, approximately one third of individuals with pediatric MS are cognitively impaired despite the early stage of disease and mild physical disability.[5-8] As in adults, dysfunction is seen in information processing speed, attention, memory and executive function. Unlike adult onset MS, language function is also often impaired in pediatric MS.[5-8]

From the Division of Neurology (KMK, PO), University of Toronto; Division of Neurology (KMK, PO), St. Michael's Hospital, Toronto, Ontario, Canada.

Received June 6, 2014. Final Revisions Submitted September 13, 2015.

Correspondence to: Kristen M Krysko, St. Michael's Hospital, 30 Bond St Room 3-007 Shuter Wing, Toronto, ON, M5B 1W8, Canada. Email: Kristen.krysko@mail.utoronto.ca.

Depression is also a common feature of adult onset MS, while there have been variable reports of the prevalence of mood disorders in pediatric MS, ranging from 6 to 46%.[6,9-12] More recent studies suggest approximately 30% of children and adolescents with pediatric MS have depression.[10-12]

Health related quality of life is reduced in adults with MS even with minimal disability,[13,14] and has been suggested to be a more comprehensive measure than disability scales in assessing the burden of MS.[15] Many factors have consistently been found to predict decreased HRQOL in adults with MS, including physical disability,[14,16-21] depression,[14,16-19,21-22] and fatigue.[14,16,18] Some studies have found that HRQOL is also predicted by cognitive dysfunction,[17,20,22] while others have found no such relationship.[14,21] When physical and mental HRQOL are analyzed independently, it has been reported that physical HRQOL is predicted by disability, depression and fatigue, while mental HRQOL is predicted only by depression and fatigue.[14,18]

There have been limited studies of HRQOL in pediatric onset MS, which have demonstrated that HRQOL is reduced during teenage years.[23-25] These limited studies have suggested that HRQOL in pediatric MS may be impacted by disability,[23,24] disease duration,[23] female gender,[23] non-white race,[23] and fatigue.[24] Additional factors that may impact HRQOL, including depression and cognition, have not been studied in pediatric onset MS.

This study aimed to assess cognition, mood and HRQOL in a group of young adults with pediatric onset MS compared to peers. These individuals have MS during their formative years while they are still developing and thus studying these factors is particularly important. Specifically, the young adult age of individuals with childhood onset MS has not been well studied. Young adulthood is an important time point to assess these individuals as it represents a critical point in life, in which one makes education, career, family and lifestyle decisions. These adults with pediatric onset MS are often competing with unaffected peers for education and employment opportunities, making comparison with peers important. We also aimed to explore the associations between these factors in a hypotheses generating explorative study with a particular interest in the relationships between disability, disease duration, cognitive impairment, depression and HRQOL in our group of young adults with pediatric onset MS.

Methods

Participants

This cross-sectional study included consecutive patients between 18 and 30 years of age with pediatric onset multiple sclerosis (onset before 18 years of age) seen at the St. Michael's Hospital adult MS clinic in Toronto between May and August 2009. These data were compared to age- and gender- matched individuals through use of normative data.

Pediatric onset MS diagnosis required onset before 18 years of age and was based on the consensus definition proposed in 2007 requiring multiple episodes of CNS demyelination in space and time that do not meet criteria for acute disseminated encephalomyelitis, with additional radiologic criteria.[26] Inclusion criteria required fluency in English. Exclusion criteria included those with another neurologic disorder or intellectual disability and those experiencing an acute relapse or steroid treatment within 30 days. Thirty-four consecutive patients with pediatric MS met criteria and were included. All participants completed written informed consent. The study was approved by the St. Michael's Hospital Research Ethics Board.

Measures

Clinical charts of patients were reviewed and interviews conducted by a medical trainee under the supervision of a certified neurologist. Demographic data, medical history and MS onset, course and treatment were collected. Demographic data included self-reported education level and ancestry. Ancestry was categorized as previously published.[27] Neurologic examination was conducted to determine the Expanded Disability Status Scale (EDSS) score.[28] This scale rates physical neurologic impairment and ranges from 0, indicating no signs or complaints of neurological dysfunction, to 10, indicating death due to MS.

Cognition was assessed using the oral Rao adaptation of the Symbol Digit Modalities Test (SDMT),[29,30] which measures information processing speed, attention and visual scanning. The SDMT includes a key with paired numbers and symbols. Individuals refer to the key to decode several lines of symbols within 90 seconds and the total number decoded correctly within this timeframe is the raw score. Higher scores indicate better cognitive functioning in the assessed domain. The oral condition in which responses are given verbally was used to limit the impact of motor slowing and incoordination. This has been shown to be a useful cognitive screening test in adult[31,32] and pediatric MS.[33,34]

Depression was assessed using the Beck Depression Inventory-II (BDI-II),[35] which is a 21 item self-reported measure that measures the presence and degree of depression in adolescents and adults. It is scored from 0 to 63, with higher scores indicating more severe depression (0-13: minimal depression, 14-19: mild depression, 20-28: moderate depression, 29-63: severe depression).

Health related quality of life was assessed using the Short Form Health Survey version 2 (SF-36v2).[36] This is a 36 item self-reported questionnaire measuring four dimensions of physical health (physical functioning, role-physical, bodily pain, general health) and four dimensions of mental health (vitality, social functioning, role-emotional, mental health), with summary scores for each (Physical Component Summary (PCS) and Mental Component Summary (MCS)). Raw scores are converted to norm-based scores with a mean of 50 and a standard deviation of 10 to allow comparison with the general population, with higher values indicating better HRQOL. Prior studies have shown there are no apparent clinically important differences between general HRQOL measures (SF-36) and disease-specific HRQOL scales (e.g. MS Quality of Life Instrument 54) in MS.[15,37] Given that the SF-36 is shorter than disease specific scales with well validated age and gender based normative data, it was chosen for this study.

Procedures

All of the above was completed following a clinic visit and took approximately 1.5 hours with breaks as necessary.

Analyses

Descriptive statistics were used to describe data using mean and standard deviation or median and range as appropriate. The 95% confidence intervals accounting for the number of interval estimates and sample size were also included for outcome measures and were compared to age- and gender- matched

https://doi.org/10.1017/cjn.2015.354 Published online by Cambridge University Press

normative means. Scores on the assessment measures were converted to z-scores based on age- and gender- matched normative data to control for these factors. For the SDMT, a z-score greater than or equal to 1.5 standard deviations lower than the age- and gender- matched normative mean was used as a cutoff for cognitive impairment in the measured domain. This has been used as a cutoff in previous studies of cognition in pediatric MS.[6-8] One-sample t-tests were also used to compare to age- and gender- matched normative data for the SDMT,[38] BDI-II,[39] and SF-36v2.[36]

Pearson correlations were calculated to determine associations between clinical factors (disease duration, EDSS), cognition (SDMT), depression (BDI-II) and HRQOL (SF-36v2 summary scores) while controlling for age and gender. We describe the relationships between these factors including correlation coefficients and discuss the clinical importance of these relationships.

Data analysis was conducted using IBM SPSS Statistics for Windows (Version 22; IBM Corp., Armonk, NY, USA). Tests were 2-sided and we applied Bonferroni corrections for multiple comparisons, with a significance level of $\alpha = 0.0019$ to account for multiple comparisons (26 comparisons; $\alpha = 0.05/26$).

Results

Participants

Thirty-four young adults with pediatric onset MS were included in the study, with 56% female and 44% male (Table 1). Mean age at the time of the study was 21.25 years (SD 2.62). Mean age at disease onset was 14.91 years (SD 2.56), with a mean disease duration of 6.26 years (SD 3.55) at the time of the study. All participants had relapsing-remitting type MS. Education level (total number of years of education) was 12 years or less in 21% and greater than 12 years in 79%. Ancestry was Caucasian in 44% and non-Caucasian in the remainder as displayed in Table 1. Median EDSS was 1.25 (range 0-6) and mean annualized relapse rate (ARR) was 0.92 (SD 0.75). Annualized relapse rate was higher in the first year of disease (2.27 SD 1.4) than the second year (0.63 SD 0.96). Most patients had monosymptomatic onset (88%) and 79% had full recovery after the first relapse. Most patients (91%) were on disease modifying therapy.

Table 1: Characteristics of patients

Characteristic	MS patients (n = 34)
Current age, years (SD)	21.25 (2.62)
Age at onset, years (SD)	14.91 (2.56)
Duration of disease, years (SD)	6.26 (3.55)
Female gender, n (%)	19 (56)
Relapsing remitting type, n (%)	34 (100)
EDSS, median (range)	1.25 (0-6)
Annualized relapse rate, relapses/year (SD)	0.92 (0.75)
Relapse rate in first year, relapses/year (SD)	2.27 (1.4)
Relapse rate in second year, relapses/year (SD)	0.63 (0.96)
Years of education, n (%)	
≤12 years	7 (21)
>12 years	27 (79)
Ancestry, n (%)	
European	15 (44)
Asian	8 (24)
South American	3 (9)
Middle Eastern	2 (6)
African	2 (6)
Aboriginal	1 (3)
Mixed	3 (9)
Initial relapse symptoms, n (%)	
Monosymptomatic	30 (88)
Polysymptomatic	4 (12)
Recovery from first relapse, n (%)	
Complete	27 (79)
Incomplete	7 (21)
On disease modifying therapy, n (%)	31 (91)

MS: multiple sclerosis; n: number; SD: standard deviation; EDSS: Expanded Disability Status Scale.

Cognition

Eighteen (53%) participants displayed cognitive impairment on the SDMT while 16 (47%) performed within 1.5 standard deviations or better than age- and gender- matched normative data[38] as shown in Table 2. Mean raw score on the SDMT was 57.71 (SD 13.75, 95% confidence interval (CI) 50.45 to 64.96), while the age- and gender- matched normative mean score was 72.41. The 95% confidence interval of our estimate did not overlap with the normative mean, suggesting a difference from normative data. This was also supported by a statistically significant one-sample t-test comparing our cohort with the age- and gender- matched normative mean (mean z-score difference −1.39, 95% CI −2.10 to −0.68, $p < 0.001$). Those with pediatric onset MS tended to score worse on the SDMT compared to peers.

Depression

According to the BDI-II measure, 27 (79%) showed minimal to no depression, 5 (15%) mild depression and 2 (6%) moderate depression. None had severe depression. The mean BDI-II score was 7.65 (SD 6.25, 95% CI 4.35 to 10.95) as shown in Table 2. The age- and gender- matched normative[39] mean (8.86) fell within this 95% confidence interval, suggesting there was no difference in BDI-II scores from normative data. This was supported by a non-significant one-sample t-test comparing our cohort with age- and gender- matched normative data[39] (mean z-score difference −0.19, 95% CI −0.56 to 0.19, $p = 0.138$).

Health related quality of life

The mean Physical Component Summary (PCS) of the SF-36v2 in young adults with pediatric onset MS was 50.54 (SD 7.14, 95% CI 46.77 to 54.31) as shown in Table 2. The age- and gender- matched normative[36] mean was 53.55, which lies near the upper limit within the 95% confidence interval of our estimate. Additionally, we did not find a statistical difference comparing our cohort to normative data with a one-sample t-test (mean z-score difference −0.40, 95% CI −0.83 to 0.04, $p = 0.007$).

https://doi.org/10.1017/cjn.2015.354 Published online by Cambridge University Press

Table 2: Scores on tests of cognitive function (Symbol Digit Modalities Test), depression (Beck Depression Inventory-II) and health related quality of life (Short Form Health Survey Version 2) compared with age- and gender- matched normative data

Measure	MS patients (n = 34)	Age- and gender- matched normative data
SDMT		
Mean raw score (SD), 95% CI	57.71 (13.75), 50.45 to 64.96*	72.41 (10.88)
≥1.5 SD from norm means with worse performance, n (%)	18 (53)	
<1.5 SD from norm means, n (%)	16 (47)	
BDI-II		
Mean score (SD), 95% CI	7.65 (6.25), 4.35 to 10.95	8.86 (7.98)
Minimal depression (0-13), n (%)	27 (79)	
Mild depression (14-19), n (%)	5 (15)	
Moderate depression (20-28), n (%)	2 (6)	
Severe depression (29-63), n (%)	0 (0)	
SF-36v2		
PCS, mean (SD), 95% CI	50.54 (7.14), 46.77 to 54.31	53.55 (9.69)
MCS, mean (SD), 95% CI	47.74 (10.79), 42.04 to 53.43	46.85 (12.52)
PF, mean (SD), 95% CI	50.41 (9.91), 45.18 to 55.64	53.30 (10.38)
RP, mean (SD), 95% CI	48.21 (9.03), 43.45 to 52.97	53.01 (9.53)
BP, mean (SD), 95% CI	54.39 (8.80), 49.75 to 59.03	52.00 (11.29)
GH, mean (SD), 95% CI	45.11 (9.81), 39.93 to 50.29	50.34 (11.77)
VT, mean (SD), 95% CI	50.71 (9.10), 45.91 to 55.51	47.68 (12.18)
SF, mean (SD), 95% CI	48.35 (10.33), 42.90 to 53.80	49.58 (11.84)
RE, mean (SD), 95% CI	47.88 (11.24), 41.95 to 53.80	50.32 (11.44)
MH, mean (SD), 95% CI	48.27 (11.41), 42.25 to 54.29	47.56 (12.78)

*$p < 0.0019$ compared to age- and gender- matched normative data.[36,38,39]
MS: multiple sclerosis; n: number; SDMT: Symbol Digit Modalities Test; SD: standard deviation; CI: confidence interval; BDI-II: Beck Depression Inventory II; SF-36v2: Short Form Health Survey version 2; PCS: Physical Component Summary; MCS: Mental Component Summary; PF: physical functioning; RP: role-physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role-emotional; MH: mental health.

Table 3: Pearson correlations between disease duration, disability, cognition, depression and quality of life controlled for age and gender

	EDSS	SDMT	BDI-II	PCS	MCS
Disease duration	0.030	−0.111	−0.067	0.114	−0.166
EDSS		−0.699*	−0.165	−0.437	0.037
SDMT			0.168	0.237	0.023
BDI-II				−0.129	−0.580*

Pearson's correlation coefficient shown for each pair of variables.
*$p < 0.0019$.
EDSS: Expanded Disability Status Scale; SDMT: Symbol Digit Modalities Test; BDI-II: Beck Depression Inventory II; PCS: Physical Component Summary; MCS: Mental Component Summary.

Those with pediatric onset MS may have somewhat lower PCS scores compared to peers, although this was not confirmed statistically. Normative[36] means fell outside of our interval estimate 95% confidence intervals for the physical domains of role-physical (RP) and general health (GH) as shown in Table 2, suggesting our group performed more poorly on these physical HRQOL domains. However, this was not supported by one-sample t-tests comparing our cohort to normative data, as these did not reach significance with the Bonferroni correction (RP mean z-score difference −0.60, 95% CI −1.20 to −0.01, $p = 0.003$; GH mean z-score difference −0.51, 95% CI −0.93 to −0.08, $p = 0.001$). Interval estimate 95% confidence intervals for the other physical domains (physical functioning, bodily pain), the Mental Component Summary and the mental domains (vitality, social functioning, role-emotional and mental health) overlapped with age- and gender- matched normative means, suggesting no difference.

Associations between cognition, mood and quality of life

We found no moderate or strong correlations between disease duration and the SDMT, BDI-II or summary scores of the SF-36v2 as shown in Table 3. Disability as measured by the EDSS revealed a strong correlation with cognition as measured by the SDMT ($r = -0.699$, $p < 0.001$). Higher EDSS was associated with worse performance on the SDMT. The EDSS includes a functional system subdomain assessing cerebral function, which may partly explain this. The correlation coefficient between EDSS

https://doi.org/10.1017/cjn.2015.354 Published online by Cambridge University Press

and the Physical Component Summary of the SF-36v2 revealed a moderate correlation but was not statistically significant ($r = -0.437$, $p = 0.009$). Higher disability was associated with poorer HRQOL. There was a negligible correlation between disability and the MCS.

Depression as measured by the BDI-II was moderately correlated with the Mental Component Summary of the SF-36v2 ($r = -0.580$, $p < 0.001$). Lower depression scores were associated with higher HRQOL scores.

There were no moderate or strong correlations between cognition (SDMT) and either summary scale of the SF-36v2 (PCS, MCS).

Discussion

This study examined a rarely studied group of young adults with pediatric onset MS at a critical point in their lives, suggesting that they have poorer cognitive function and lower physical HRQOL in some domains compared to peers despite relatively mild physical disability, while depression and mental HRQOL were similar. Physical HRQOL may be related to disability, while mental HRQOL may be related to depression.

Our group of young adults with pediatric onset MS had characteristics similar to other studies of pediatric MS, with high relapse rates early in the disease but many had complete recovery from early relapses and mild physical disability.[3,4] As previously reported during childhood and adolescent stages of pediatric MS,[5-8] we found young adults with pediatric MS had poor information processing speed. Fifty-three percent were impaired on the SDMT, which is higher than rates of cognitive impairment reported in previous studies, which estimate that cognitive impairment occurs in about one third of children and adolescents with pediatric MS.[6,8] This may be partly due to the longer disease duration in our study due to the adult age group. Additionally, we used a single test as a screen for cognitive impairment, while studies have typically required impairment on two or more cognitive domains to be considered cognitively impaired. However, the SDMT has been suggested to be an excellent cognitive screen in both adult[31,32] and pediatric[33,34] onset MS. To limit required testing time, we assessed only one domain as a marker for cognition, given we were also assessing mood and HRQOL.

Cognitive impairment had a strong association with disability, with poorer cognition associated with worse disability, but cognition was not associated with disease duration. A relationship between cognition and EDSS has been reported in pediatric MS,[6,7,34] although other studies have not found support for this relationship.[8,33] This relationship may partly be explained by the cerebral functional system subdomain which is part of the EDSS score. Similarly, some longitudinal studies in pediatric MS have shown significant worsening of cognition over two years,[7,9] while others have not replicated this finding.[40] It has been suggested that cognition may be particularly impacted in pediatric MS due to onset of MS during a critical stage of central nervous system development and important educational years, in addition to a neurodegenerative component of MS.[5,8,9]

We found that 21% of patients displayed mild to moderate depression, which is lower than recent reports of depression rates in pediatric MS, which suggest about 30% have depression.[10-12] However, reported rates have varied widely, from 6 to 46%.[6,9-12]

There was a non-significant reduction of physical HRQOL, but not mental HRQOL, compared to peers in our young adults with pediatric MS, despite low disability and short disease duration. This is similar to other studies assessing self-reported HRQOL in teenagers with pediatric MS, which have found reductions in physical and psychosocial, but not emotional, domains of HRQOL.[23-25]

Poorer physical HRQOL displayed a moderate relationship with higher disability, while poorer mental HRQOL showed a moderate relationship with higher depression scores, with a stronger relationship between mental HRQOL and depression. Two prior studies of pediatric MS assessed the impact of demographics, disability and disease duration on both self- and parent- reported HRQOL.[23,24] Similar to our study, these found that disability was related to total[23] and physical but not emotional HRQOL.[24] Similar to MacAllister and colleagues,[24] we did not find a relationship between disease duration and HRQOL. Mowry and colleagues[23] reported that non-white race was associated with reduced total self- and parent- reported HRQOL and that older age, disease duration and female gender were associated with poorer parent-reported HRQOL. We did not replicate these findings of the relationship between longer disease duration and poorer HRQOL. However, this may only be related to parent-reported HRQOL, which we did not assess. MacAllister and colleagues[24] also reported an impact of fatigue on physical and emotional health, which we did not assess.

This is the first study in young adults with pediatric MS assessing the relationships between cognition, depression and HRQOL. We found a robust relationship between depression and mental HRQOL, which has been reported consistently in adult MS.[14,16-19,21-22] We did not find a relationship between cognition and HRQOL, which has been a debated topic in adult MS with some studies supporting a relationship,[17,20,22] and others finding no relationship.[14,21]

There are several limitations to the present study. Firstly, the study was cross-sectional and correlations cannot be considered to represent causation. However, this study was meant to be exploratory and hypotheses generating with confirmatory longitudinal studies required. Secondly, there was no control group and instead comparisons were made with age- and gender-matched normative data. Although this is not ideal, comparison with normative data still provides meaningful information clinically. Young adults with pediatric MS are often competing with individuals free of disease for education and employment opportunities. Thus, understanding the impact of MS on cognition, mood and HRQOL during these formative years compared to normative data may help provide insight into challenges faced by this group despite relatively mild physical disability. Understanding the relationship between these factors may provide targets for intervention aimed at improving HRQOL, such as treatment of depression. Additional studies with control groups are needed. Comparison of these factors in pediatric MS with adult onset MS would also be interesting to determine whether the onset of MS during important developmental years differentially impacts these factors, but this was not addressed in the present study. Thirdly, given the study was conducted at a tertiary center there was possible selection bias as only those referred to a tertiary center were included, so the sample may not be representative of the entire pediatric MS population. Fourthly, we did not include non-English speaking individuals due to an

https://doi.org/10.1017/cjn.2015.354 Published online by Cambridge University Press

inability to complete outcome measures. This could have led to certain ethnicities not being included, thus also potentially impacting generalizability.

Additionally, our small sample size did not allow for multiple regression analyses to control for potential confounders due to limited power, so results must be interpreted with caution. Given our small sample size, this study had low observed power, which may have resulted in inappropriately negative findings. Given the low power, we relied more on interpretation of 95% confidence intervals and correlation coefficient values rather than hypothesis testing. The aim of this study was hypotheses generation and given the low power, we cannot draw firm conclusions from this study. Larger studies are required for further investigation of these findings. Furthermore, there were many comparisons made given the exploratory nature of the study, which was meant to generate hypotheses for future confirmatory studies. Thus, we provide our results with Bonferroni corrections to highlight statistically significant results. Future more robust studies are necessary to evaluate the hypotheses generated by this study.

Additionally, we did not include an assessment of fatigue, which, since our study was conducted, has been shown to impact HRQOL in pediatric MS. Furthermore, we only assessed cognition in one domain; however, the SDMT has been suggested to be an appropriate cognitive screen in MS.[31-34] Finally, we used a general HRQOL measure rather than a disease specific measure. However, prior studies have suggested there are no clinically important differences between disease specific and general QOL scales,[15,37] suggesting the SF-36 was an adequate measure of HRQOL.

This is the first study specifically comparing individuals with pediatric MS at a young adult stage to peers, thus with a longer duration of disease than many prior studies. We find support for reductions in cognition and a suggestion of reduced physical HRQOL compared to peers in this stage of pediatric onset MS. Cognition and physical HRQOL may be related to disability, while mental HRQOL may be related to depression. In the care of adults with pediatric onset MS, it is important to assess and address cognition and mood in addition to physical disability, with the goal of improving HRQOL. Further studies including longitudinal studies and studies with control groups and comparison with adult onset MS are needed to confirm these hypotheses. Further studies are also needed to assess these factors later in the course of the disease and should include measures of fatigue to determine its impact on HRQOL. Longitudinal studies could also explore the impact of various interventions on cognition, depression and HRQOL.

Acknowledgements

This project was funded through the University of Toronto's Comprehensive Research Experience for Medical Students (CREMS) program.

Disclosures

Kristen Krysko has the following disclosure: Comprehensive Research Experience for Medical Students (CREMS) program, Salary for 3 months of research (no ongoing salary support). Paul O'Connor has the following disclosures: He has received consulting fees and honoraria from Biogen Idec, Sanofi Genzyme, EMD Serono, Novartis, Genentech and Teva Neuroscience. He has also received research support from Biogen Idec, Sanofi Genzyme, Novartis and Genentech.

References

1. Duquette P, Murray TJ, Pleines J, et al. Multiple sclerosis in childhood: clinical profile in 125 patients. J Pediatr. 1987;111:359-63.
2. Chitnis T, Glanz B, Jaffin S, Healy B. Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. Mult Scler. 2009;15:627-31.
3. Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. Arch Neurol. 2009;66:54-9.
4. Renoux C, Vukusic S, Mikaeloff Y, et al. Natural history of multiple sclerosis with childhood onset. N Engl J Med. 2007;356:2603-13.
5. Banwell BL, Anderson PE. The cognitive burden of multiple sclerosis in children. Neurology. 2005;64:891-4.
6. MacAllister WS, Belman AL, Milazzo M, et al. Cognitive functioning in children and adolescents with multiple sclerosis. Neurology. 2005;64:1422-5.
7. MacAllister WS, Christodoulou C, Milazzo M, Krupp LB. Longitudinal neuropsychological assessment in pediatric multiple sclerosis. Dev Neuropsychol. 2007;32:625-44.
8. Amato MP, Goretti B, Ghezzi A, et al. Cognitive and psychosocial features of childhood and juvenile MS. Neurology. 2008;70:1891-7.
9. Amato MP, Goretti B, Ghezzi A, et al. Cognitive and psychosocial features in childhood and juvenile MS: two year follow-up. Neurology. 2010;75:1134-40.
10. Goretti B, Ghezzi A, Portaccio E, et al. Psychosocial issue in children and adolescents with multiple sclerosis. J Neurol Sci. 2010;31:467-70.
11. Weisbrot DM, Ettinger AB, Gadow KD, et al. Psychiatric comorbidity in pediatric patients with demyelinating disorders. J Child Neurol. 2010;25:192-202.
12. Parrish JB, Weinstock-Guttman B, Smerbeck A, Benedict RHB, Yeh EA. Fatigue and depression in children with demyelinating disorders. J Child Neurol. 2012;28:713-8.
13. Pugliatti M, Riise T, Nortvedt MW, et al. Self-perceived physical functioning and health status among fully ambulatory multiple sclerosis patients. J Neurol. 2008;255:157-62.
14. Klevan G, Farbu E, Jacobsen CO, et al. Health related quality of life in patients recently diagnosed with multiple sclerosis. Acta Neurol Scand. 2014;129:21-6.
15. Nortvedt MW, Riise T, Myhr KM, Nyland HI. Quality of life in multiple sclerosis: measuring the disease effects more broadly. Neurology. 1999;53:1098-103.
16. Amato MP, Ponziani G, Rossi F, Liedl CL, Stefanile C, Rossi L. Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. Mult Scler. 2001;7:340-4.
17. Benito-Leon J, Morales JM, Rivera-Navarro J. Health-related quality of life and its relationship to cognitive and emotional functioning in multiple sclerosis patients. Eur J Neurol. 2002;9:497-502.
18. Benedict RHB, Wahlig E, Bakshi R, et al. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality and behavior change. J Neurol Sci. 2005;231:29-34.
19. Hopman WM, Coo H, Edgar CM, McBride EV, Day AG, Brunet DG. Factors associated with health-related quality of life in multiple sclerosis. Can J Neurol Sci. 2007;34:160-6.
20. Fernandez O, Baumstarck-Barrau K, Simeoni MC, Auquier P. Patient characteristics and determinants of quality of life in an international population with multiple sclerosis: Assessment using the MusiQoL and SF-36 questionnaires. Mult Scler. 2011;17:1238-49.
21. Baumstarck-Barrau K, Simeoni MC, Reuter F, et al. Cognitive function and quality of life in multiple sclerosis patients: a cross-sectional study. BMC Neurol. 2011;11:17.
22. Glanz BI, Healy BC, Rintell DJ, Jaffin SK, Bakshi R, Weiner HL. The association between cognitive impairment and quality of life in patients with early multiple sclerosis. J Neurol Sci. 2010;290:75-9.

23. Mowry EM, Julian LJ, Im-Wang S, et al. Health-related quality of life is reduced in pediatric multiple sclerosis. Pediatr Neurol. 2010;43:97-102.
24. MacAllister WS, Christodoulou C, Troxell R, et al. Fatigue and quality of life in pediatric multiple sclerosis. Mult Scler. 2009;15:1502-8.
25. Ketelslegers IA, Catsman-Berrevoets CE, Boon M, et al. Fatigue and depression in children with multiple sclerosis and monophasic variants. Eur J Neurol. 2010;14:320-5.
26. Krupp LB, Banwell B, Tenembaum S, et al. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. Neurology. 2007;68(Suppl 2):S7-12.
27. Kennedy J, O'Connor P, Sadovnick AD, Perara M, Yee I, Banwell B. Age at onset of multiple sclerosis may be influenced by place of residence during childhood rather than ancestry. Neuroepidemiology. 2006;26:162-7.
28. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33: 1444-52.
29. Smith A. Symbol Digits Modalities Test. Los Angeles: Western Psychological Services; 1982.
30. Rao SM. A manual for the brief repeatable battery of neuropsychological tests in multiple sclerosis. New York: National MS Society; 1990.
31. Parmenter BA, Weinstock-Guttman B, Garg N, Munschauer F, Benedict RHB. Screening for cognitive impairment in multiple sclerosis using the Symbol Digit Modalities Test. Mult Scler. 2007;13:52-7.
32. Langdon DW, Amato MP, Boringa J, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Mult Scler. 2012;18:891-8.
33. Smerbeck AM, Parrish J, Serafin D, et al. Visual-cognitive processing deficits in pediatric multiple sclerosis. Mult Scler. 2011;17:449-56.
34. Charvet LE, Beekman R, Amadiume N, Belman AL, Krupp LB. The Symbol Digit Modalities Test is an effective cognitive screen in pediatric onset multiple sclerosis (MS). J Neurol Sci. 2014;341: 79-84.
35. Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. San Antonio: Psychological Corporation; 1996.
36. Ware JE Jr, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. User's Manual for the SF-36v2 Health Survey, 2nd ed. Lincoln: QualityMetric Incorporated; 2007.
37. Moore F, Wolfson C, Alexandrov L, Lapierre Y. Do general and multiple sclerosis-specific quality of life instruments differ? Can J Neurol Sci. 2004;31:64-71.
38. Yeudall LT, Fromm D, Reddon JR, Stefanyk WO. Normative data stratified by age and sex for 12 neuropsychological tests. J Clin Psychol. 1986;42:918-46.
39. O'Hara MM, Sprinkle SD, Ricci NA. Beck Depression Inventory-II: College population study. Psychol Rep. 1998;82:1395-401.
40. Charvet LE, O'Donnell EH, Belman AL, et al. Longitudinal evaluation of cognitive functioning in pediatric multiple sclerosis: report from the US Pediatric Multiple Sclerosis Network. Mult Scler. 2014;20:1502-10.

https://doi.org/10.1017/cjn.2015.354 Published online by Cambridge University Press