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Treatment adherence and transitioning youth in pediatric multiple sclerosis

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KEYWORDS
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Abstract
Background: Transitioning youth with multiple sclerosis (MS) represent a vulnerable group to potentially poor outcomes. It is unknown how pediatric MS patients transition into adult care.
Objectives: To describe self-management skills that include adherence to disease-modifying therapies, quality of life measures, illness perception, transition readiness and healthcare skills assessments in patients with pediatric MS and associations with clinical and cognitive outcomes.
Methods: This is a prospective cross-sectional study at the pediatric MS center and transitional MS clinic at the University of California, San Francisco. Patients and one of their parents completed validated surveys for self-management skills. Non-adherence is defined as not taking their medication more than 20% of the time in the past 1 month. Wilcoxin matched-pairs rank test and McNemar's tests were used for comparison of patient and parent responses. Univariate and multivariate regression models were used for analyses adjusting for disease duration and socio-economic status.
Results: Thirty patients were enrolled with a mean ($\pm$SD) age of 15.8 years $\pm$2.8, 53% was female and 47% Hispanic. The rate of non-adherence was 37%. The most common reason for non-adherence was forgetting to take their medication reported in 50% of patients. In adjusted regression models, higher EDSS was associated with a lower score on patient's quality of life (13 points decrease, 95% CI 6–18, $p<0.0001$), and lower healthcare skills (15 points decrease, 95% CI 5–26, $p=0.006$). Four points increase in Symbol Digit Modalities Test score was associated a 0.1 increase in transition readiness score (95% CI 0.07–0.2, $p=0.001$) and 3.9 points increase in healthcare skills scores (95% CI 1.7–6, $p=0.008$).

Abbreviations: QOL, Quality of life; DMT, Disease modifying therapy; UCSF, University of California, San Francisco; Ped QOL, Pediatric Quality of Life Inventory; TRAQ, Transition readiness assessment questionnaire; HCAQ, Healthcare skills assessment questionnaire; SES, Socioeconomic status; SDMT, Symbol Digit Modalities Test; EDSS, Expanded Disability Status Scale

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Conclusions: It is important to recognize clinical and cognitive status of pediatric MS patients as these may be critical in their ability to transition to adult care.

1. Introduction

Multiple sclerosis (MS) onset occurs before age 18 in up to 10% of all MS cases (pediatric MS) (Krupp et al., 2007, S7–S12; Renoux et al., 2007, 2603–2613). These patients develop disability at a younger age, and face substantial impact on their quality of life and functional outcomes for a longer period of time (Mowry et al., 2010, 97–102).

Adherence to treatment and medication routines is a critical health maintenance skill for successful transition from pediatric to adult care. Self-management skills also involve maintaining quality of life (QOL), managing and attending doctor visits, and problem solving around health-related issues. Transitioning youth with chronic medical conditions represent a vulnerable group that may carry over their health habits into adulthood (Blum et al., 1993, 570–576). This is especially true for pediatric MS considering life-long therapies and the need for at least annual clinic visits (Lublin et al., 2014, 278–286).

Poor adherence to medication regimens is associated with worse disease outcomes in adult-onset MS (Patti, 2010, 1–9). A previous study evaluated disease modifying therapy (DMT) discontinuation rather than adherence rates in pediatric MS patients (Thannhauser et al., 2009, 119–123). Thus, adherence and how adherence and self-management skills influence clinical outcomes are unknown in young patients with MS. Identifying modifiable behaviors and predictors of poor adherence is critical to maximize best MS outcomes.

We sought to characterize self-management attributes in pediatric MS including transitioning care into adulthood. We used validated questionnaires completed by the patient and one of the parents to identify possible discordance between reports. We also describe associations between self-management and clinical outcomes in pediatric MS that may be important to develop future interventions in this age group.

2. Methods and subjects

2.1. Study design

This is a cross-sectional study of prospectively enrolled patients from the University of California San Francisco (UCSF) pediatric MS center and MS transition clinic. The research protocol was approved by the UCSF Committee on Human Research and written informed consent was obtained from parents and patients aged 18 years and older. Assent was also obtained from all patients younger than 18 years of age.

2.2. Study subjects

Inclusion criteria include: 1) a diagnosis of MS according to the International Pediatric Multiple Sclerosis study group criteria (Krupp et al., 2013, 1261–1267), 2) age at enrollment between 12 and 23 years with disease onset before 18, 3) patients with at least 2 prior visits at the UCSF pediatric and/or transitional MS clinics, and 4) taking a self-administered DMT for at least 3 months. We chose this age group because the process of preparing youth with chronic health conditions and disabilities for the transition to adult care typically starts in early adolescence (American Academy of Pediatrics and American Academy of Family Physicians, and American College of Physicians-American Society of Internal Medicine, 2002, 1304–1306).

Exclusion criteria include a diagnosis of developmental disorders that could interfere with the patient's ability to follow instructions and cognitive testing. Patients or parents who were not fluent in English were also excluded, as questionnaires used were not validated in other languages.

2.3. Questionnaires completed

The patient and one parent completed the Pediatric Quality of Life Inventory (Ped QOL) (Nortvedt et al., 1999, 1098–1103), Brief Illness Perception Questionnaire (IPQ) (Broadbent et al., 2006, 631–637) and an adherence questionnaire (Bruce et al., 2010, 112–120) at the time of their routine clinic visits (Supplementary Table 1). Patients additionally completed the healthcare skills related questionnaire, which includes the Transition readiness assessment questionnaire (TRAQ) (Sawicki et al., 2011, 160–171). Parents also completed a health care skills assessments questionnaire (HCAQ) (Hackworth and McMahon, 1991, 69–85) (Supplementary Table 1). We defined non-adherence as missing DMTs more than 20% of the time in the past month (Lu et al., 2008, 86–94). We selected a 1 month time period to avoid recall bias (Lu et al., 2008, 86–94). Parents self-reported ethnicity and completed socio-economic status (SES) questionnaires. SES was calculated using participating parent and partner's education level, employment, and total household income (Thakur et al., 2013, 1202–1209). This information was dichotomized into low versus medium/high SES.

2.4. Clinical and demographic data

Patients underwent brief neuropsychological evaluation with the verbal form of the Symbol Digit Modalities Test (SDMT) at the time of their visit (Charvet et al., 2014, 79–84). We collected clinical data including the presence of at least one relapse in the past year, Expanded Disability Status Scale (EDSS), and disease duration at the time of enrollment by medical records review.

2.5. Data management and statistical analysis

Questionnaires completed on paper forms were entered into REDCap Software-Version 5.5.11-© 2013 Vanderbilt University

hosted by UCSF (Harris et al., 2009, 377–381). Statistical analyses were performed using STATA/SE 12.1. Although total questionnaire scores were normally distributed, individual questions analyzed were not. We therefore used Wil coxin matched-pairs sign rank test to compare medians of continuous variables. We used McNemar's test to compare dichotomous variables of patient and parent responses. Logistic regression models were used for non-adherence associations with patient demographics, clinical, cognitive and psychometric measures. Univariate and multivariate regression models were used to assess associations between psychometric measures and clinical outcomes.

Table 1 Patient demographics and clinical features stratified by adherence.

	Total $N=30$	Adherent $N=19$	Non-adherent $N=11$
Age (years), *mean*±*SD*	15.8±2.5	16.2±2.5	15.3±2.4
Proportion of females, *n* (%)	16 (53)	9 (47)	7 (64)
Ethnicity, *n* (%) Hispanic	14 (47)	10 (53)	4 (36)
Race, *n* (%)			
White	13 (43)	9(47)	4 (36)
American Indian/Alaska native	0	0	0
African American	2 (7)	0	2 (18)
Asian/Pacific Islander	4 (13)	1 (5)	2 (18)
Mixed	3 (10)	2 (11)	1 (9)
Unknown	9 (30)	7 (37)	2 (18)
Low socioeconomic status, *n* (%)	15 (50)	11 (58)	4 (36)
Disease duration (years), *median* (*IQ range*)	2.5 (0.9, 7.6)	1.8 (0.9, 4.4)	5.2 (2.5, 6)
Duration of current DMT in months, *median* (*IQ range*)	10 (3, 54)	8 (3, 30)	22 (15, 29)
EDSS, *median* (*IQ range*)	1.5 (1, 3)	1.5 (1, 2.5)	1.5 (1, 2)
Relapses present in the past year, %	17 (57)	14 (74)	3 (27)
DMT used, *n (%)*			
Interferon β-1a IM	5 (17)	5 (26)	0
Interferon β-1a SC	4 (13)	2 (11)	2 (18)
Interferon β-1b SC	4 (13)	2 (11)	2 (18)
Glatiramer acetate	14 (47)	8 (42)	6 (55)
Dimethylfumarate	2 (7)	1 (5)	1 (9)
Mycophenolate mofetil	1 (3)	1 (5)	0

IQ: interquartile; DMT: disease modifying therapy; EDSS: Expanded Disability Status Scale.

Table 2 Reported number of responses for non-adherence and reasons for missing doses of disease-modifying therapy in the past month among 30 patient/parent pairs.

	Patients only	Parents only	Both	Neither	*p*-Value[a]
Non-adherence reported	4	2	7	17	0.7
Reason for missing disease modifying therapy					
Forget to take their medication	6	1	9	14	0.1
Medications Interfere with their activities	1	3	1	25	0.6
Medication causes bruising and/or hurts	1	4	2	23	0.4
Patients are afraid of needles	0	3	1	26	0.3
Medications cause side effects	5	2	2	21	0.5
Parents forget to give them their medication	0	0	4	26	1
Patients want to ignore their condition	0	8	3	19	**0.008**
Patients do not think they need it	2	5	1	22	0.5
Financial reasons	0	0	1	29	1
Patients ran out of their medication	2	0	2	26	0.5

Non-adherence defined as missing their medication more than 20% of the time in the past 1 month reported on a visual analog scale questionnaire. Patients may forget to take their medication occasionally and yet be considered adherent if they do not miss more than 20% of their doses.

[a]McNemar's test.

3. Results

3.1. Patient and parent characteristics

A total of 30 subjects fulfilled inclusion criteria and were enrolled in the study between July 2012 and April 2014. All questionnaires were complete except for two patients who missed some questions in the transition readiness assessment questionnaire and one parent form that were missing three of the quality of life questions. Data from adherence questionnaires were complete.

Mean age of patients was 15.8±2.8 years. Patients enrolled were 53% female and 47% Hispanic. Median disease duration was 2.5 (interquartile range 0.9–7.6) and 17 patients (57%) had at least one relapse in the past year (Table 1). Subjects were primarily on injectable therapies except for three-of whom two were on dimethylfumarate and one was on mycophenolate mofetil. In non-adherent subjects, mean age was 15.3±2.4 years of whom 64% was females and 36% Hispanic (Table 1). The mother completed the parent survey in 77% of the cases. Mean age of the parent completing the survey was 46±7.8 years.

3.2. Causes of non-adherence

Non-adherence was self-reported in 37% of patients versus 30% of parents. This discordance was not statistically significant for non-adherence report ($p=0.7$, McNemar's test, Table 2). Since non-adherence was defined as those who miss more than 20% of their medication, patients who missed some doses but were adherent also completed reasons for non-adherence questions as did their parents. Patients reported the most common cause for non-adherence as forgetting to take their medication (reported in 50% of patients versus 33% of parents, Table 2). There were no systemic differences between patient and parent's reports for the reasons for missing doses except for discordance in parents' reports who thought their children wanted to ignore their disease and therefore missed their medication ($p=0.008$, Table 2).

Table 4 Non-adherence associations with patient demographics, clinical, cognitive and psychometric measures (logistic regression).

	Odds ratio (95% CI)	*p*-Value
Patient demographics		
Age (years)	0.8 (0.6, 1.2)	0.3
Female sex	1.9 (0.4, 8.9)	0.4
Hispanic ethnicity	0.5 (0.1, 2.4)	0.4
Low SES	0.4 (0.1, 1.9)	0.3
Clinical		
Disease duration (per 1 year increase)	1.02 (0.99, 1.04)	0.09
Duration of therapy (per 1 month increase)	1.03 (0.99, 1.07)	0.1
Presence of at least one relapse in the past year	0.1 (0.03, 0.7)	**0.02**
EDSS (per 1.0 increase in EDSS)	0.99 (0.4, 2.5)	0.99
Cognitive		
SDMT (per one point increase)	1.01 (0.95, 1.06)	0.8
Psychometric measures		
Quality of life (per one point increase)	0.99 (0.95, 1.04)	0.8
Illness perception (per one point increase)	1.2 (0.6, 2.2)	0.6
Transition readiness (per one point increase)	0.6 (0.3, 1.5)	0.3

SES: socioeconomic status; EDSS: Expanded Disability Status Scale; SDMT: Symbol Digit Modalities Test.

Table 3 Median scores for psychometric surveys completed.

Median scores (interquartile range)	Patient	Parent[a]	*p*-Value[b]
Quality of life scores 0 (worst)-100 (best)			
Totals	53.8 (36.1, 64.1)	51.3 (29.3, 63)	0.36
Physical	53.1 (36.3, 68.8)	59.4 (29.4, 68.8)	0.49
Psychosocial	51 (40, 61.7)	45.4 (30, 61.7)	0.08
Illness perception questionnaire scores 0 (best)-10 (worst)	4.6 (3.6, 5.1)	5.6 (4.1, 6.6)	0.02
Transition readiness assessment questionnaire scores 0 (worst)-5 (best)			
Total	2.7 (2.3, 3.3)	-	
Self-management	2.2 (1.8, 3.6)	-	
Self-advocacy	3.5 (2.8, 3.9)	-	
Healthcare skills scores 0 (worst)-100 (best)	-	40.8 (28.4, 67.2)	

[a]The mother completed the parent survey in 23 patients, while the father completed 7 parent surveys.
[b]Wilcoxin matched-pairs rank test.

3.3. Psychometric scores

Patients and their parents scored similarly on the total ped QOL but median scores tended to be lower in psychosocial aspects in the parents' (51 (IQ range 40, 62)) versus patients' reports (45 (IQ range 30, 62), $p=0.08$, Table 3). Parents had a more threatening view of their child's MS as represented by their higher median illness perception scores 5.6 (IQ range 4.1, 6.6) versus 4.6 (IQ range 3.6, 5.1) in patients ($p=0.02$). This was mostly driven by parents reporting more concern and lack of personal control from MS in their children than the patients reported ($p=0.0001$ and $p=0.005$ respectively, Supplementary Table 2). The parents also reported less benefit from their use of DMT as compared to their children ($p=0.04$).

3.4. Clinical associations

The presence of at least one relapse in the past year was associated with lower odds of non-adherence in the past year (OR 0.1, 95% CI 0.03, 0.7; $p=0.02$). Patients' age, sex, ethnicity and SES were not associated with non-adherence (Table 4).

Table 5 details results for adjusted and unadjusted regression analyses for psychometric measures and clinical outcomes. All analyses were adjusted for disease duration and socioeconomic status. Analyses that included SDMT also adjusted for patients' age. In univariate regression models, one point increase in EDSS score was associated with a lower score on patients' QOL (13 points decrease, 95% CI 7-18, $p<0.0001$), and lower health care assessment scores (13 points decrease, 95% CI 3-24, $p=0.015$). One point increase on cognitive testing with SDMT, increased transition readiness scores by 0.04 (95% CI 0.02-0.06, $p=0.001$) and healthcare assessment scores by one point (95% CI 0.4-1.5, $p=0.001$, Table 5).

The association between cognitive testing and transition readiness scores was mostly driven by the self-management part of the questionnaire rather than self-advocacy (Table 5). There were no associations between illness perception and clinical outcomes. Adjusting for disease duration and socioeconomic status did not significantly alter these results. Higher cognitive scores were associated with higher QOL but not when adjusting for patients' age (Table 5).

4. Discussion

Our results highlight that young patients with higher disability and worse cognitive functioning may be the ones with more difficulty transitioning to adult care. Our finding

Table 5 Unadjusted and adjusted regression models for psychometric tests and clinical and cognitive measures.

	Unadjusted		Adjusted[a]	
	Change in score per unit increase (95% CI)	*p*-Value	Change in score per unit increase (95% CI)	*p*-Value
QOL total				
EDSS	−12.7 (−18.2, −7.2)	**<0.001**	−12 (−17.8, −6.3)	**<0.001**
SDMT	0.4 (0.02, 0.8)	**0.04**	0.3 (−0.1, 0.7)	0.2
QOL physical				
EDSS	−16 (−25, −8.6)	**<0.001**	−15.4 (−23.7, −7)	**0.001**
SDMT	0.5 (−0.02, 1.1)	0.06	0.4 (−0.2, 1)	0.2
QOL psychosocial				
EDSS	−10.5 (−15.4, −5.6)	**<0.001**	−10.2 (−15.4, −5)	**<0.001**
SDMT	0.3 (−0.003, 0.7)	0.05	0.2 (−0.1, 0.6)	0.2
IPQ				
EDSS	0.4 (−0.2, 0.9)	0.2	0.4 (−0.2, 0.9)	0.2
SDMT	0.002 (−0.03, 0.04)	0.9	−0.005 (−0.04, 0.03)	0.8
TRAQ total				
EDSS	−0.4 (−0.8, −0.02)	**0.04**	−0.4 (−0.9, −0.01)	**0.047**
SDMT	0.04 (0.02, 0.06)	**0.001**	0.03 (0.008, 0.05)	**0.009**
TRAQ self-management				
EDSS	−0.5 (−0.9, 0.05)	0.08	−0.5 (−1.03, 0.05)	0.07
SDMT	0.04 (0.01, 0.06)	**0.006**	0.03 (0.0004, 0.06)	**0.047**
TRAQ self-advocacy				
EDSS	−0.3 (−0.7, 0.07)	0.09	−0.3 (−0.7, 0.1)	0.2
SDMT	0.02 (−0.004, 0.04)	0.1	0.02 (−0.01, 0.04)	0.2
HCAQ				
EDSS	−13.2 (−23.6, −2.7)	**0.015**	−15.4 (−26.1, −4.8)	**0.006**
SDMT	1 (0.4, 1.5)	**0.001**	0.7 (0.2, 1.1)	**0.008**

QOL: quality of life; EDSS: Expanded Disability Status Scale; SDMT: Symbol Digit Modalities Test; IPQ: illness perception questionnaire; TRAQ: transition readiness assessment questionnaire; HCAQ: healthcare skills assessment questionnaire.

[a]Adjusted results for disease duration and socioeconomic status. Results for SDMT were adjusted for disease duration, socioeconomic status and patient age.

of association between a screening test of cognitive function and readiness to transition to adult care is clinically relevant as a four point change in the SDMT in adult MS is associated with loss of employment (Morrow et al., 2010, 1131–1145). These findings are most salient for adolescents with pediatric MS as they embark into adulthood with considerations for employment, education and quality of life. Our results are concerning as they suggest that most teenagers with MS do not appear ready to be fully involved in their care.

Our findings that greater disability was associated with reports of lower quality of life are consistent with our previous findings in pediatric MS (Mowry et al., 2010, 97–102) and suggest the cohort in the current study matches previously described ones.

We found that about 37% of pediatric MS patients taking self-administered therapies report non-adherence with forgetfulness as the most common reason for missing their medication. Our non-adherence rates to DMTs are slightly higher than published adult MS rates (Ruggieri et al., 2003, 361–364; Devonshire et al., 2011, 69–77). Although studies related to pediatric MS adherence are not available for comparison, other comparable studies on adherence in pediatric patients with chronic diseases show similar reasons (Bugni et al., 2012, 483–488) with forgetfulness as the most common reason for missing doses.

Interestingly, non-adherence was associated with a relapse-free history in the past year but not associated with other demographic or clinical measures. Even though one of the main goals of MS therapies is the absence of relapses, having no relapses may result in decreased patient recognition of their condition and more forgetfulness of their medication. Of note, the presence of a relapse during the previous year may not be due to non-adherence as some patients had not received a full year of treatment before enrolling in this study. Finally, we cannot rule out that having fewer relapses results in fewer visits to the neurologist and possibly fewer opportunities for support and counseling on adherence.

Our data show some discrepancies between patients and parent reports. For example, parents had a more threatening view of their children's MS or the patients had a more positive outlook on their disease as compared to their parents. In addition, parents under estimated non-adherence.

Our study has several strengths including its emphasis on a topic very rarely studied in the past and the careful collection of parental and patient's reports, and clinical and cognitive measures. We also acknowledge a few limitations including small sample size and cross-sectional nature. Further, non-adherence was assessed for the past month and therefore may not reflect usual behavior.

Our study provides critical information that fills some gaps in our knowledge of adherence and self-management attributes in pediatric MS. We describe adherence characteristics in this patient population and offer some insight into the reasons for non-adherence and compare concordance with parent's responses. Our findings may not be generalizable to all pediatric MS patients as we excluded patients whose parents were not fluent in English and patients on monthly infusions of natalizumab who may have a higher disease burden and neurological disability.

5. Conclusions

Our results highlight the potential need to individualize methods used for implementation programs for transitioning youth based on their disability and cognitive status. Implementation of these programs may lead to a more successful transition to adulthood and possibly to better MS outcomes on the long term. Finally, with the advent of new therapies, it will be of interest to also investigate whether patterns of adherence will change with oral agents or agents self-injected less frequently.

Conflict of interest

No conflicts of interest for authors and this work.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.msard.2014.09.088.

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