Psychiatric diagnoses and cognitive impairment in pediatric multiple sclerosis

Deborah Weisbrot[1], Leigh Charvet[2], Dana Serafin[2], Maria Milazzo[2], Thomas Preston[2], Rebecca Cleary[2], Tiffany Moadel[2], Michelle Seibert[2], Anita Belman[2] and Lauren Krupp[2]

Abstract

Background: Pediatric multiple sclerosis (MS) represents approximately 5% of the MS population; information regarding clinical features is slowly accumulating. Cognitive and psychiatric impairments frequently occur, but remain poorly understood.

Objectives: To describe psychiatric diagnoses among children with MS referred for psychiatric assessment and their relation to cognitive impairment.

Methods: Forty-five pediatric MS patients (aged 8 to 17 years) were referred for outpatient psychiatric evaluation including a psychiatric interview (K-SADS), a clinician-based global assessment of functioning (Children's Global Assessment Scale, CGAS), a neurologic examination including the Expanded Disability Status Scale (EDSS), and a neuropsychological test battery.

Results: The most common categories of psychiatric diagnoses were anxiety disorders (*n*=15), attention deficit hyperactivity disorder (ADHD, *n*=12), and mood disorders (*n*=11). Cognitive impairment was classified in 20/25 (80%) of patients meeting criteria for a psychiatric disorder versus 11/20 (55%) of those without psychiatric disorder (*p*=0.08). Those diagnosed with anxiety or mood disorder had the highest frequency of cognitive impairment, with a significantly higher rate when compared with those with psychiatric diagnoses in other categories (*p*=0.05).

Conclusions: A variety of psychiatric diagnoses can occur in children with pediatric MS. Many of these children also had cognitive impairment, particularly those in the mood and anxiety groups.

Introduction

Children and adolescents with multiple sclerosis (MS) represent an uncommon patient population accounting for only 5% or less of those with MS, a disease much more typical of young to middle aged adults.[1] Although information concerning the neurological characteristics of pediatric MS is slowly accumulating, data regarding the comorbid psychiatric features of these children are limited.[2] The findings to date show that a variety of psychiatric disorders can occur.[2-6] For example, among 39 Italian children and adolescents with MS evaluated with structured psychiatric interviews, major depression was noted in 15%, and overall 30% had a mood disorder.[6]

Cognitive deficits are found in approximately one-third of children with MS.[4,5,7,8] This finding has been generally consistent across a variety of samples, despite differing approaches to the definition of impairment.[4,5,7,9] Little is known regarding the overlap between cognitive impairment and psychiatric disorders in pediatric MS. Among adults with MS, psychiatric disturbance has been linked to a

[1]Department of Psychiatry and Behavioral Sciences, Stony Brook University Medical Center - Division of Child and Adolescent Psychiatry, USA.
[2]Stony Brook University Medical Center Department of Neurology - Lourie Center for Pediatric Multiple Sclerosis, USA.

Corresponding authors:
Deborah Weisbrot, Department of Psychiatry and Behavioral Sciences, Stony Brook University Medical Center, Putnam Hall South Campus, Stony Brook, New York 11794-8790, USA.
Email: Deborah.Weisbrot@stonybrook.edu

Lauren Krupp, Department of Neurology, Stony Brook University Medical Center, HSC Level 12, Room 020, Stony Brook, NY 11794-8121, USA.
Email: lauren.krupp@stonybrook.edu

heightened risk of cognitive impairment. For example, individuals with adult MS and depression perform significantly worse on a working memory task than those with MS but without depression.[10]

Understanding the psychiatric correlates of pediatric MS and their association with cognitive impairment is needed to improve the recognition and prompt treatment of these issues. Here, we report on the findings of 45 children seen at a US pediatric MS center who received a psychiatric evaluation as well as a comprehensive neurological assessment and neuropsychological testing.

Participants

Between September 2006 and September 2011, a total of 150 children under 18 years old diagnosed with clinically isolated symptom (CIS) or MS according to the International Pediatric MS Study Group criteria[11] were evaluated at the Lourie Center for. All patients seen at the Center undergo a comprehensive neurological assessment and baseline neuropsychological testing. At this time, 45 children from this group were also scheduled to undergo psychiatric evaluation at the request of family or physicians. The families were offered referral if the nurse noted psychological stressors during the clinical history portion of a telephone screening interview or if the family otherwise requested consultation when offered this option. Hence, participants selected for the psychiatric evaluation were a non-consecutive sample. The study was approved by the Stony Brook Institutional Review Board; a parent provided consent, and all participants signed assent forms.

Measures

Psychiatric diagnoses

A child and adolescent psychiatrist (DW) administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-PL[12]), a semi-structured psychiatric diagnostic interview. The K-SADS-PL is a commonly used diagnostic instrument in psychiatric assessment. The K-SADS-PL interviews require that a highly trained interviewer decide whether an item is satisfactorily fulfilled or whether further questions are required to get the relevant information. The K-SADS generates reliable and valid child psychiatric diagnoses with test-retest reliability coefficients in an excellent range for present and/or lifetime diagnoses of major depression, any bipolar, generalized anxiety, conduct, and oppositional defiant disorder (0.77-1.00) and in a good range for present diagnoses of posttraumatic stress disorder and ADHD (0.63-0.67).[12,13]

Children's Global Assessment Scale (CGAS)

The Children's Global Assessment Scale (CGAS) is a global measure of social and psychiatric functioning for children aged 4-16 years. It is widely used in clinical and research settings. It uses a range of scores from 1 to 100 and has anchors at 10-point intervals including descriptions of psychopathology and functioning for each interval. The CGAS is based on an adaptation of the Global Assessment Scale (GAS) for adults. The joint reliability has been tested in research and clinical settings and ranges from 0.83 to 0.91.[14]

Expanded Disability Status Scale (EDSS)

The EDSS is a standard, accepted neurologic impairment measure in multiple sclerosis. It quantifies impairment in eight functional systems: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and ambulation.[15]

Neuropsychological testing

All participants completed a standardized battery of neuropsychological tests at a time when they were neurologically stable and relapse free for 30 or more days. Participants at the time of testing also had to be off steroids for at least 30 days. All measures were administered by a clinical neuropsychologist or a trained and supervised psychometrician using standardized procedures. The battery was administered in approximately 2.5 hours and children were given breaks when needed.

The following tests were included in the battery: Wechsler Abbreviated Scale of Intelligence (WASI: 4 subtest IQ),[16] Wechsler Intelligence Scale for Children IV (WISC-IV: Digit Span),[17] Contingency Naming Test (CNT: Total Time, Total Efficiency),[18] Continuous Performance Test II (CPT-II: omissions, commissions, hit response time),[19] Delis-Kaplan Executive Function System Trail Making Test (DKEFS Trails: Conditions 1 through 5),[20] Tower of London (TOL: total moves, total correct, rule violations, total time),[21] California Verbal Learning Test-Child/Second edition (CVLT-C/II: total trials, list B, short delay free recall, long delay free recall),[22] Beery Visual-Motor Integration Test (VMI: total score),[23] Rey Osterrieth Complex Figure Test (ROCF: copy, short delay, long delay),[24] Expressive One Word Vocabulary Test (EOWVT: total score),[25] Delis-Kaplan Executive Function System Verbal Fluency (DKEFS letter and category fluency: total score).[20]

Impairment ratings of each neuropsychological test were estimated using published age-stratified normative data to calculate individual *z*-scores. We adopted the traditional benchmark definition for mild impairment as previously applied,[8,26] which was a score falling at least one standard deviation (SD) below the normative mean. The number of test scores falling below average was tabulated for each participant. A composite z score of the scores on the entire neuropsychological battery was also calculated for every participant. They were classified as having a cognitive impairment if 20% or more of their completed test scores or if their composite z score fell at least one SD below the

Table 1. Psychiatric disorders diagnosed in sample.[a]

Anxiety disorders	Frequency n (%)
Anxiety disorder NOS	4 (16)
Generalized anxiety disorder	2 (8)
Obsessive-compulsive disorder	1 (4)
Panic disorder	1 (4)
Posttraumatic stress disorder	3 (12)
Specific phobia	1 (4)
Social anxiety disorder	3 (12)
Mood disorders	
Adjustment disorder with mixed or depressed mood	2 (8)
Bipolar disorder NOS	1 (4)
Depressive disorder NOS	3 (12)
Dysthymic disorder	1 (4)
Major depressive episode or disorder	4 (16)
Mood disorder caused by a general medical condition	1 (4)
Other psychiatric disorders	
Attention deficit hyperactivity disorder (all types)	12 (48)
Oppositional defiant disorder	2 (8)
Tourette's disorder	1 (4)
Reactive attachment disorder	1 (4)
Relational problem (parent-child)	3 (12)

[a]Most participants (17 of 25 or 68%) met criteria for two or more diagnoses.
NOS: Not Otherwise Specified.

normative average. Psychiatric diagnoses were tabulated according to DSM-IV-TR categories.

Statistics

Frequency analyses determined the proportion of those with cognitive impairment according to category of psychiatric diagnosis. A regression analysis was used to determine the contribution of disease-related and psychiatric factors to participants' cognitive functioning.

Results

A total of 29 females and 16 males, ranging in age from 8.4 to 17.0 years with a mean of 15.3 ± 2.0 years were evaluated. Thirty-one children were Caucasian, 10 were African American, and four were other races. A total of nine were of Hispanic ethnicity. Neurologic disability, as measured by the EDSS,[15] ranged from 0 to 4, with a mean of 1.44 ± 1.27. Psychiatric evaluation was completed within an average of 2 months of obtaining the EDSS (mean 0.15 ± 0.42 years).

Twenty-five of the 45 participants (56%) met criteria for at least one psychiatric diagnosis, with the majority of those receiving at least two or more diagnoses (17 of 25 or 68%). The diagnostic categories most frequently found in the sample were anxiety disorders (*n*=12), attention deficit

hyperactivity disorder (ADHD, *n*=12), and mood disorders (*n*=11). Table 1 shows the individual disorders that were identified. Overall, anxiety or mood disorders were present in 20 of the 25 (80%) children with a psychiatric diagnosis.

For the total group, 31 of 45 (69%) met criteria for cognitive impairment. Level of impairment was significantly associated with the expanded disability status score (r=-0.47, p=0.002), whereas age was not (r=-23, p=0.13). The composite neuropsychological index ranged from -1.87 to 1.04, with a mean of z=-0.31±0.66.

As shown in Table 2, when the children were divided into two groups of those with or without at least one psychiatric disorder, they did not significantly differ in age, gender, race, or neurologic characteristics (e.g. EDSS or annual relapse rate). A greater proportion of Hispanic patients met diagnostic criteria for a psychiatric disorder (p=0.03, Fisher's exact test). Twenty participants (80%) with a psychiatric disorder versus 11 (55%) without a psychiatric disorder met criteria for cognitive impairment (p=0.11, Fisher's exact test). Patients with either a mood or anxiety disorder had a lower (worse) neuropsychological composite z-score (-0.59 ± 0.7) than those with other categories of disorders (-0.10 ± 0.6; p=0.02), and had a higher proportion of failed tests (49.1 ± 26.1 vs. 31.8± 21.3; p=0.02).

As shown in Figure 1, there was a higher proportion of patients with cognitive impairment in the mood and anxiety group compared with those with other psychiatric disorders (p=0.05, Fisher's exact test). The mood or anxiety group also showed a trend for a greater frequency of cognitive impairment compared with the no psychiatric diagnosis group (p=0.08). There was no difference in the proportion of cognitive impairment between the no psychiatric disorder group compared with the other psychiatric disorder group (p=0.6). General level of functioning, as measured by the CGAS rating, was significantly poorer in the group with a mood or anxiety disorder (56.75 ± 15.4) compared with those without a mood/anxiety disorder (83.60± 13.4; p<0.01), as well as those with no psychiatric diagnosis (88.50 ± 8.1; p < 0.01). However, there were no differences in mean CGAS scores between those with and without cognitive impairment.

Multiple linear regression analysis was used to develop a model for predicting the participant's level of cognitive functioning (percent of tests scoring below average) from their disease duration (in years), EDSS (as a measure of overall neurological disability), and CGAS scores (as a measure of overall psychiatric dysfunction). This model accounted for 32% of the total variance in cognitive functioning F (3,38) = 5.94, p =0.002, R^2 = .32. Both predictor variables of EDSS (β=0.44, CI 3.25-13.87, p=0.002) and CGAS (β =-0.34, CI -0.84 to -0.15, p=0.006) but not disease duration, had significant partial effects. Therefore, as would be expected, more severe EDSS scores and more impaired CGAS levels predicted poorer cognitive functioning.

**Table 2.** Clinical features of children with and without a psychiatric disorder.

	Psychiatric disorder (n=25)	**No psychiatric disorder (n=20)**	p[a]
Demographic descriptors			
Age mean (SD)	15.43 (±1.9)	15.23 (±2.0)	0.73
Female n (%)	16 (64)	13 (65)	0.95
Race n (%)			0.34[b]
Caucasian	19 (76)	12 (60)	
African-American	5 (11)	5 (11)	
Asian	0	1 (2)	
Mixed/other	1 (2)	2 (4)	
Hispanic ethnicity n (%)	8 (32%)	1 (5%)	**0.03**[b]
Parent education mean (SD)	13.29 (±2.86)	14.48 (±2.3)	0.13
Clinical characteristics			
Age symptom onset years mean (SD)	13.85 (±2.87)	13.94 (±2.3)	0.97
Disease duration years mean (SD)	1.53 (±1.39)	1.30 (±1.4)	0.57
EDSS mean (SD)	1.61 (±1.37)	1.24 (±1.15)	0.35
Annual relapse rate (SD)	1.26 (±0.82)	1.15 (±0.80)	0.64
Cognitive and psychiatric functioning			
CGAS (SD)	58.20 (±15.0)	88.50 (±8.1)	**<0.001**
WASI FSIQ-4 subtest (SD)	100 (±12.6)	106.3 (±13.3)	0.11
Cognitive impairment (≥20% below average test measures) n (%)	20 (80%)	11 (55%)	0.11[b]

WASI Full 4 is a composite index of WASI Vocabulary, Similarities, Block Design and Matrix Reasoning.
CGAS: Children's Global Assessment Scale; EDSS: Expanded Disability Status Scale.
[a]*p* values reported from *t*-test comparisons.
[b]Exception of *p* value for Fisher's exact test for categorical variables.
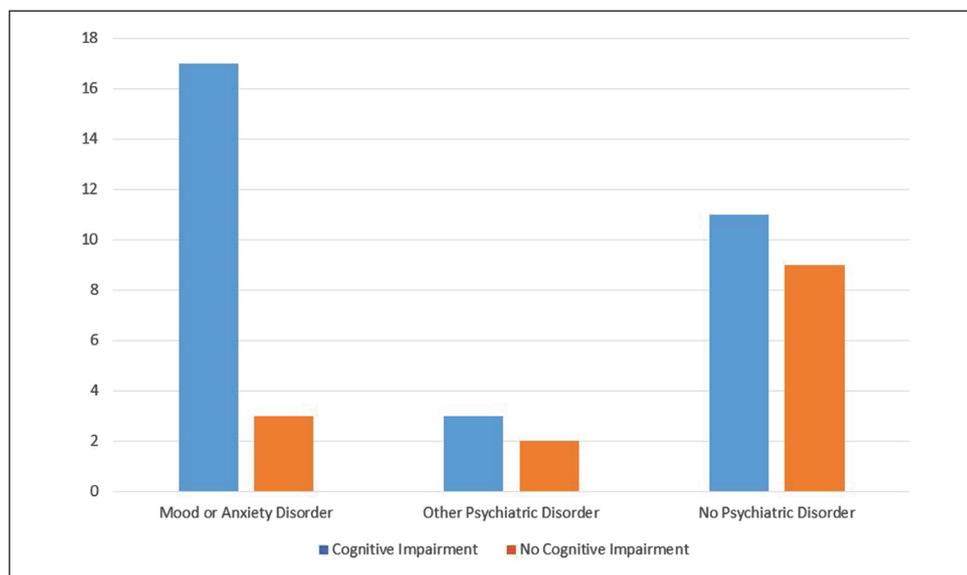
Figure 1. Co-occurrence of psychiatric disorders and cognitive impairment.
No psychiatric disorder vs. mood or anxiety disorder: *p*=0.05.

Discussion

We found a variety of psychiatric diagnoses among 45 pediatric MS patients who underwent psychiatric assessment. Of the 25 children with a psychiatric disorder, more than two-thirds had more than one psychiatric diagnosis The most frequent psychiatric diagnoses. were anxiety disorders, mood disorders, and ADHD. It was not possible to predict, from the neurologic findings, which patients were most likely to have a psychiatric diagnosis as there were no differences in

those with or without a psychiatric disorder in age at symptom onset, disease duration, EDSS, annual relapse rate, or proportion with cognitive impairment.

Children with concurrent mood or anxiety disorders compared with those with other psychiatric diagnoses had a higher frequency of cognitive dysfunction. The concurrence of mood or anxiety disorders and cognitive impairment raises the possibility that depression and anxiety symptoms were associated with decreased attention and information processing, therefore adversely affecting performances on the cognitive measures. Similarly, the presence of cognitive impairment in a child or adolescent who was previously functioning well in school is a situation which often leads to emotional distress in its own right and suggests that adverse mood could also be reactive to incurring cognitive deficits. Alternatively, anxiety or mood disorders and cognitive deficits may be independent manifestations of the underlying demyelinating CNS disease. Of concern is that most of these pediatric MS patients had their psychiatric and cognitive problems diagnosed relatively early in their course of illness, that is during the first 1 to 2 years of their disease, and over time more difficulties could emerge. Longitudinal studies are needed to assess the long-term risk for and consequence of psychiatric illness in pediatric MS.

Chronic disorders such as diabetes, sickle cell disease, and cystic fibrosis have been shown to be a significant risk for psychiatric illness in children and adolescents.[27–29] When the illness has a central nervous system component, the risk is even greater.[27,28] Children and adolescents with MS and their families are already confronting the extraordinarily difficult and potentially overwhelming demands associated with having a demyelinating disorder in childhood or adolescence. This study suggests that concurrent cognitive and psychiatric problems are additional potential concerns. Early recognition and treatment for these conditions is key as the more difficult and refractory these psychiatric disorders and cognitive impairments become to address, the greater the risk for behavioral problems including school avoidance/refusal, academic failure, and substance/alcohol abuse.[30–32] Psychiatric disorders and cognitive impairment can further compromise academic functioning, resulting in lifetime economic and social repercussions[27,29,33] and lead to poorer health outcomes and lower medication compliance.[34]

This study had several limitations. Only a subset of patients evaluated at the Center underwent psychiatric evaluation and were most frequently those referred because of suspected psychosocial stressors or requested by the family after learning it was available. The selection process likely biased our findings towards higher rates of psychiatric diagnoses and prevents generalization from this study of prevalence rates of psychiatric diagnoses in pediatric MS. Additionally, the timeline of psychiatric diagnoses was not established to allow for comparison with MS symptom onset. Therefore, it is not clear if in some cases psychiatric symptoms developed before MS disease activity. We also did not examine the possible influence of a positive family history of psychiatric disorder.

Future studies will need to follow a larger unselected prospective series. Additional work is needed to measure the relation between cognitive, psychiatric, and neuroimaging findings and to determine the role of sub-threshold symptoms of anxiety, depression, and impulse control disorders.

Overall, our findings make it clear that psychiatric disturbance and cognitive impairment can co-exist in pediatric MS. Identification of cognitive impairment should increase the clinician's concern that depression or anxiety may also be present. Similarly, it is critical to recognize that those with mood or anxiety disorders might also be experiencing cognitive impairment.

Acknowledgement

Conflict of interest

The authors declare no conflicts of interest.

Funding

References

1. Chitnis T, Glanz B, Jaffin S and Healy B. Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. *Mult Scler* 2009; 15: 627–631.
2. Weisbrot DM, Ettinger AB, Gadow KD, et al. Psychiatric comorbidity in pediatric patients with demyelinating disorders. *J Child Neurol* 2010; 25: 192–202.
3. MacAllister WS, Boyd JR, Holland NJ, et al. The psychosocial consequences of pediatric multiple sclerosis. *Neurology* 2007; 68: S66–69.
4. Amato MP, Goretti B, Ghezzi A, et al. Cognitive and psychosocial features of childhood and juvenile MS. *Neurology* 2008; 70: 1891–1897.
5. Amato MP, Goretti B, Ghezzi A, et al. Cognitive and psychosocial features in childhood and juvenile MS: two-year follow-up. *Neurology* 2010; 75: 1134–1140.
6. Goretti B, Ghezzi A, Portaccio E, et al. Psychosocial issue in children and adolescents with multiple sclerosis. *Neurolog Sci* 2010; 31: 467–470.
7. Till C, Ghassemi R, Aubert-Broche B, et al. MRI correlates of cognitive impairment in childhood-onset multiple sclerosis. *Neuropsychology* 2011; 25: 319–332.
8. Julian L, Serafin D, Charvet L, et al. Cognitive impairment occurs in children and adolescents with multiple sclerosis: Results from a United States network. *J Child Neurol* 2013; 28: 102–107.

9. MacAllister WS, Belman AL, Milazzo M, et al. Cognitive functioning in children and adolescents with multiple sclerosis. *Neurology* 2005; 64: 1422–1425.

10. Arnett PA, Higginson CI, Voss WD, et al. Depression in multiple sclerosis: relationship to working memory capacity. *Neuropsychology* 1999; 13: 546–556.

11. Krupp LB, Banwell B and Tenembaum S. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. *Neurology* 2007; 68: S7–12.

12. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997; 36: 980–988.

13. Chambers WJ, Puig-Antich J, Hirsch M, et al. The assessment of affective disorders in children and adolescents by semistructured interview. Test-retest reliability of the schedule for affective disorders and schizophrenia for school-age children, present episode version. *Arch Gen Psychiatry* 1985; 42: 696–702.

14. Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). *Arch Gen Psychiatry* 1983; 40: 1228–1231.

15. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444–1452.

16. The Psychological Corporation. *The Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: Harcourt Assessment, 1999.

17. Wechsler D. *The Wechsler Intelligence Scale for Children*. San Antonio, TX: The Psychological Corporation, 1991.

18. Anderson P, Anderson V, Northam E and Taylor H. Standardization of the Contingency Naming Test: A measure of Reactive Flexibility. *Clin Neuropsycholog Assess* 2000; 1: 247–273.

19. Homack S and Riccio C. Connors' Continuous Performance Test (2nd ed.; CCPT-II). *J Attention Dis* 2006; 9: 556–558.

20. Delis D, Kaplan E and Kramer J. *Delis-Kaplan Executive Function System*. San Antonio: The Psychological Corporation, Harcourt Brace & Company, 2001.

21. Culbertson C and Zillmer EA. *Tower of London Drexel University (TOL DX): Technical manual*. North Tonawanda, NY: Multi-Health Systems Inc., 2001.

22. Delis D, Kramer JH, Kaplan E and Ober BA. *California Verbal Learning Test (2nd ed.)*. San Antonio, TX: Psychological Corporation, 2000.

23. Beery K and Beery NA. *The Beery-Buktenica Developmental Test of Visual-Motor Integration - 5th Edition*. Minneapolis, MN: NCS Pearson, Inc., 2006.

24. Rey A and Osterrieth P. Translations of excerpts from Rey's 'Psychological Examination of Traumatic Encephalopathy' and Osterrieth's 'The Complex Figure Test'. *The Clinical Neuropsychologist* 1993; 7: 2–21.

25. Brownell R. *Expressive One-Word Picture Vocabulary Test Manual*. Novato, CA: Academic Therapy Publications, 2000.

26. Trittschuh EH, Crane PK, Larson EB, et al. Effects of varying diagnostic criteria on prevalence of mild cognitive impairment in a community based sample. *J Alzheimers Dis* 2011; 25: 163–173.

27. Schatz J, Brown RT, Pascual JM, et al. Poor school and cognitive functioning with silent cerebral infarcts and sickle cell disease. *Neurology* 2001; 56: 1109–1111.

28. King AA, White DA, McKinstry RC, et al. A pilot randomized education rehabilitation trial is feasible in sickle cell and strokes. *Neurology* 2007; 68: 2008–2011.

29. Pinckney RB and Stuart GW. Adjustment difficulties of adolescents with sickle cell disease. *J Child Adolesc Psychiatr Nurs* 2004; 17: 5–12.

30. Angold A, Costello EJ and Erkanli A. Comorbidity. *J Child Psychol Psychiatry* 1999; 40: 57–87.

31. Last CG and Strauss CC. School refusal in anxiety-disordered children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1990; 29: 31–35.

32. Hawkins JD, Catalano RF and Miller JY. Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: Implications for substance abuse prevention. *Psychol Bull* 1992; 112: 64–105.

33. Evans D, Foa EB, Gur RE, et al (eds). *Treating and Preventing Adolescent Mental Health Disorders: What We Know and What We Don't Know*. New York: Oxford University, 2005.

34. Freudenberg N and Ruglis J. Reframing school dropout as a public health issue. *Preventing Chronic Dis* 2007; 4: A107.