Chronic fatigue syndrome in adolescents

Beyond tiredness

VATHSALA AGARWALLA MB BS, DCH, MPH, FRACP
ALEXANDRA RUSHWORTH BA(Psych)(Hons), MClinPsych
SUSAN TOWNS MB BS, MMH, FRACP

Chronic fatigue syndrome (CFS) in adolescents can have significant physical, social and psychological impacts. A comprehensive history and assessment and exclusion of other fatigue-causing conditions are crucial to timely diagnosis. An individualised multidisciplinary rehabilitative approach to adolescents with CFS is key to management.

Chronic fatigue syndrome (CFS) in adolescents is a condition primarily characterised by severe, persistent, unexplained fatigue.[1] In CFS, the fatigue is exacerbated by exertion (postexertional malaise) and may be accompanied by other symptoms including musculoskeletal pain, cognitive 'brain fog', unrefreshing or disturbed sleep, and neurological and autonomic symptoms such as headache and dizziness on standing or exertion consistent with orthostatic intolerance.[2] There are many proposed hypotheses for the aetiology of CFS including infectious agents, immune dysfunction, autoimmune disorders, genetic susceptibility or abnormality, neuroendocrine disorders, circulatory abnormalities, toxins, metabolic disturbances, or a combination of these.[2,3] The estimated national incidence of paediatrician-diagnosed cases of CFS in adolescents aged 10 to 17 years in Australia is 6.38 per 100,000 per year.[1] Adolescence has been identified as one of two age peaks in incidence of CFS in a Norwegian-based population registry study.[4] Diagnostic criteria are based on commonly used case definitions for the diagnosis of CFS/myalgic encephalomyelitis (ME) in children and adolescents and are discussed in detail below.[5-7]

CFS in adolescents is frequently triggered by a viral or infective illness, with about two-thirds of paediatric patients identified as having a presumed viral or infective trigger for symptom onset.[1] In addition to severe fatigue, adolescents with CFS may present to their general practitioner with nonspecific symptoms, including frequent sore throats, headaches or pain, or because of concerns regarding decreased level of functioning, school attendance, decreased engagement with their regular activities or with friends.[2]

CFS in adolescents typically occurs during middle to late adolescence, during a critical period of social, emotional and physical development.[8] Disruption during this key stage of development can be associated with significant functional impairment, such as decreased school attendance, impaired social participation and emergence of comorbid mental health conditions including depression and anxiety, as well as long-term health, social, emotional and vocational implications.[2,8] There is often a protracted period of time between symptom onset and the diagnosis being made, with 52% of children or adolescents diagnosed 13 months after symptom onset.[1] Timely diagnosis is important to ensure appropriate medical care and management and to minimise the long-term morbidity of CFS.[9]

Adolescents have a relatively good prognosis compared with adults with CFS. Adolescents engaged in multidisciplinary rehabilitative treatment have shown significant improvements in parent-reported adolescent physical and psychosocial functioning

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Dr Agarwalla is a Paediatrician and Staff Specialist in Adolescent Medicine, Department of Adolescent Medicine, Sydney Children's Hospital Network, Sydney. Ms Rushworth is a Clinical Psychologist, and Co-lead of the Complex Adolescent Clinic, Department of Adolescent Medicine, Sydney Children's Hospital Network, Sydney. Associate Professor Towns is Head of Adolescent Medicine for The Sydney Children's Hospitals Network; a Consultant Paediatrician, Department of Respiratory Medicine, The Children's Hospital at Westmead, Sydney; and Clinical Associate Professor, Discipline of Paediatrics and Child Health, Faculty of Medicine, The University of Sydney, Sydney, NSW.

over time.[10] Of those seen in a specialised Australian adolescent CFS service, 50% reported recovery from CFS, with 38% recovering within five years and 68% within 10 years.[11] All improved functionally, with only 5% reporting remaining very unwell.[11] Supportive professionals who made or understood the diagnosis were highly valued by young people with CFS, highlighting the importance of accurate diagnosis and therapy.[12]

Assessment and diagnosis

Since it was first described by Holmes in 1988,[13] the terminology surrounding CFS has often been confusing, with various clinical criteria and case definitions described. Commonly used terminology includes myalgic encephalomyelitis (ME) and the umbrella term of CFS/ME.[6] The diagnosis of CFS/ME is a clinical diagnosis, based on thorough history, recognition of the pattern of symptoms and exclusion of other conditions causing fatigue, through comprehensive history-taking, physical examination and appropriate medical investigations.[2] Diagnosis is based on the young person fulfilling diagnostic criteria. A number of varied clinical criteria are currently used to diagnose CFS in children and adolescents, including the 1994 Fukuda case definition for CFS/ME adopted by the Centers for Disease Control and Prevention, the 2015 Institute of Medicine Diagnostic Criteria for Children and Adults, and the 2006 Canadian Paediatric Clinical Case Definition for CFS/ME, which is best used for research purposes.[5,6,14] The Fukuda criteria remain the most commonly cited case definition for CFS;[15] however, this definition was predominantly designed for use in adults. More recently formulated case definitions were designed for children and adolescents.[6,8,14,16] Commonly used case definitions/clinical criteria are outlined in the Table.

Common across these criteria are the presence of the following three core features:

- postexertional malaise (following cognitive or physical exertion)
- unrefreshing sleep
- significant fatigue that is severe, of new onset and not substantially alleviated by rest, with reduction of function compared with before illness.

Other core features seen in adolescents include cognitive impairment and autonomic dysfunction/orthostatic intolerance.[2,6,7] Importantly, the case definition requirement for CFS is typically a duration of illness of more than three months for adolescents compared with more than six months for adults.[7]

Assessment should also include the identification of predisposing factors, such as genetic factors, family history and joint hypermobility, as well as complicating factors such as orthostatic intolerance, sleep disturbance, and anxiety and mood disorders, as outlined below.[2]

Physical signs in CFS are subtle and are not diagnostic.[2] Physical examination should include growth parameters and pubertal staging, an orthostatic standing test to assess for orthostatic intolerance, Beighton score to assess joint hypermobility (Figure) and musculoskeletal signs.[2] There is no current valid, reliable laboratory test for diagnosing CFS, and baseline blood tests are usually normal. Recommended initial investigations according to main symptomatology are outlined in the Box.[7]

UK guidelines on CFS/ME diagnosis and management recommend that children and adolescents presenting with a history suggestive of CFS be referred to a paediatrician within six weeks of assessment and have the diagnosis confirmed by a paediatrician.[7] For children or young people with significant functional impairment associated with fatigue, referral to a paediatrician or adolescent physician should not be delayed.

Assessment and management of complications and comorbidities

A number of conditions commonly associated with CFS in children and adolescents can predispose to and exacerbate the fatigue, most notably postural orthostatic tachycardia syndrome (POTS) and clinical joint hypermobility. Functional gastrointestinal disorders, chronic persistent widespread pain, headaches, sleep disturbance, depression and anxiety are also frequently reported.[1]

Orthostatic intolerance/postural orthostatic tachycardia syndrome (POTS)

Orthostatic intolerance refers to symptoms that worsen with upright posture and improve with lying down.[2,17] Symptoms of orthostatic intolerance include lightheadedness or dizziness, whiteout or blackout of visual fields, blurred vision, headaches, nausea and increased fatigue. Signs on physical examination include acrocyanosis or mottling of the dependent limbs and facial pallor with standing for more than a few minutes.[2] The most common syndromes of orthostatic intolerance are POTS, neurally mediated hypotension and orthostatic hypotension, the latter two being less frequent in the paediatric/adolescent population.[2]

POTS is a form of autonomic dysfunction, characterised by orthostatic intolerance, excessive postural tachycardia and fatigue.[18] It is the most common comorbid condition in paediatric CFS and is present in 26.2% of paediatric patients diagnosed with CFS in Australia.[1] Therefore, accurate identification and management of POTS is important as part of management of CFS in children and adolescents.

To diagnose POTS, a 10-minute orthostatic standing test should be undertaken as follows: with the adolescent resting supine for at least 5 minutes, record a baseline heart rate and blood pressure when supine; then ask them to stand while you measure heart rate and blood pressure every minute for 10 minutes. The diagnosis of POTS requires the presence of orthostatic signs and/or symptoms (such as lightheadedness, dizziness, syncope, visual disturbance, nausea, headache,

TABLE. COMMONLY USED CASE DEFINITIONS FOR THE DIAGNOSIS OF CFS/ME IN CHILDREN AND ADOLESCENTS

	Centers for Disease Control and Prevention Fukuda Criteria for CFS (1994)[5]	Institute of Medicine Criteria for ME/CFS (2015)[6] (and criteria for systemic exertion intolerance syndrome)	National Institute of Clinical Excellence Criteria for CFS (2007)[7]
Primary criteria*	All of the following symptoms must be present: • Clinically evaluated, unexplained, persistent or relapsing chronic fatigue • New or definite onset • Not the result of ongoing exertion • Not substantially alleviated by rest • Results in substantial reduction in previous levels of occupational, educational, social or personal activities	Requires all three of the following: • Substantial reduction/impairment in ability to engage in pre-illness level of occupational, educational, social or personal activities • Persists for >6 months* and is accompanied by fatigue OR • Fatigue is profound, new or definite onset, not a result of ongoing exertion and not substantially alleviated by rest • Post-exertional malaise • Unrefreshing sleep	Fatigue with all of the following features: • New or specific onset • Persistent and/or recurrent • Unexplained by other conditions • Has resulted in a substantial reduction in activity level • Characterised by postexertional malaise/fatigue (typically delayed i.e. after 24 hours and takes some days to recover)
Additional criteria	Four or more of the following symptoms (present for ≥6 months) and not predating the fatigue: • Substantial impairment in short-term memory or concentration • Sore throat • Tender cervical or axillary lymph nodes • Muscle pain • Multijoint pain without joint swelling or redness • Headaches of a new type, pattern or severity • Unrefreshing sleep • Postexertional malaise lasting >24 hours	At least one of the following two manifestations is also required: • Cognitive impairment • Orthostatic intolerance	At least one of the following: • Sleep disturbance • Generalised muscle and/or joint pain, without evidence of inflammation • Headaches • Painful lymph nodes without pathological enlargement • Sore throat • Cognitive dysfunction • Physical or mental exertion makes symptoms worse • General malaise or 'flu-like' symptoms • Dizziness and/or nausea • Palpitations in the absence of identified cardiac pathology
Exclusions	Any of the following: • Any active medical condition that may explain the presence of chronic fatigue • Concurrent/previous diagnosis of major depressive disorder with psychotic or melancholic features • Substance abuse • Severe obesity		• Other conditions that could cause fatigue

Abbreviations: CFS = chronic fatigue syndrome; ME = myalgic encephalomyelitis.
* For children and adolescents, a diagnosis can be made if symptoms have been present for ≥3 months.

palpitations), as well as an increase in heart rate of 40 bpm or more when going from supine to upright posture, and a heart rate sustained at over 120 bpm.[2,18,19] The co-occurrence of POTS and fatigue needs to be identified in order for concurrent management of POTS and CFS and to prevent increased functional impairment. POTS is often associated with joint hypermobility, functional gastrointestinal disorders, sleep disturbance and mood disorders, which can complicate CFS.[19] Undiagnosed POTS is associated with significant social and emotional consequences, including decreased function, school attendance and engagement with extracurricular activities, multiple health care visits, increased carer burden and missed work for parents.[18]

Management of POTS includes non-pharmacological strategies of increasing fluid and salt intake to maintain intravascular volume, use of compression

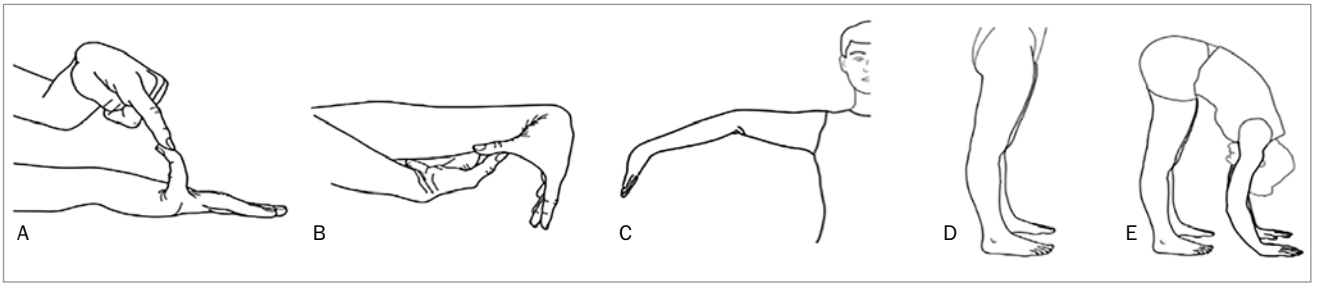

Figure. The Beighton Scoring System. Each joint is measured with a goniometer and each side is scored independently, with 1 point scored if the below are positive.
(A) With the palm of the hand and forearm resting on a flat surface with the elbow flexed at 90°, if the metacarpal-phalangeal joint of the fifth finger can be hyperextended more than 90° with respect to the dorsum of the hand, it is considered positive.
(B) With arms outstretched forward but hand pronated, if the thumb can be passively moved to touch the ipsilateral forearm it is considered positive.
(C) With the arm outstretched to the side and hand supine, if the elbow extends more than 10° it is considered positive.
(D) While standing, with knees locked in genu recurvatum, if the knee extends more than 10° it is considered positive.
(E) With knees locked straight and feet together, if the patient can bend forward to place the total palm of both hands flat on the floor just in front of the feet it is considered positive.
Images and caption courtesy of Dr Birgit Juul-Kristensen, University of South Denmark, Odense M, Denmark.

stockings when standing, incorporation of aerobic and strengthening exercises and re-engagement with academic activity in a graded fashion.[18] Pharmacological interventions should be targeted at improving the dominant symptoms that do not respond to conservative measures. Pharmacological interventions for orthostatic intolerance/POTS include: medications that increase blood volume such as fludrocortisone and the combined oral contraceptive pill; sympathetic tone modifiers such as propranolol, clonidine and vasoconstricting agents (e.g. midodrine); and selective serotonin reuptake inhibitors such as fluoxetine or sertraline, which have the added benefit of treating concurrent depression or anxiety.[2]

Joint hypermobility

Joint hypermobility is commonly associated with CFS and 60% of young patients who meet the criteria for CFS/ME also have joint hypermobility (compared with 20% of healthy adolescents).[2] An Australian cohort of paediatrician-diagnosed cases of CFS found that 13% had associated joint hypermobility.[1]

Adolescents presenting with symptoms suggestive of CFS should be assessed for generalised joint hypermobility (GJH). If GJH is present, screening for Ehlers-Danlos syndrome (EDS), particularly hypermobile EDS (hEDS), should be undertaken, as a subset of individuals with CFS may have hEDS as the underlying aetiology.[20] Diagnosing joint hypermobility is important, as the condition can add to the burden of illness in CFS/ME and requires different approaches in physical therapy.[2]

Joint hypermobility is best assessed through the use of the Beighton Score during physical examination (Figure). A score of 5 or greater in adolescents is indicative of GJH. If joint hypermobility is present, history and examination looking for signs of hEDS (using the detailed diagnostic criteria for EDS subtypes outlined in the 2017 international classification of the Ehlers-Danlos Syndromes[21]) should be undertaken to ensure that appropriate management is recommended. The recommended management for joint hypermobility is physical strengthening, stabilising joints with maintenance of healthy muscle and reconditioning to prevent injury and musculoskeletal pain, in conjunction with pain management and psychological strategies to prevent distress.[22]

Sleep disturbance

Adolescents commonly present to primary care providers with nonspecific symptoms of tiredness and fatigue. Screening questions for sleep difficulties in adolescents should be included in the initial work-up of a fatigued adolescent. Sleep disorders including delayed sleep phase disorder, obstructive sleep apnoea, narcolepsy, idiopathic hypersomnolence and periodic leg movement in sleep need to be excluded or treated appropriately.[23,24] Consider referral to a sleep specialist and formal polysomnography if there are concerns regarding diagnosis or ongoing issues with sleep with significant impact on function despite instituting adequate sleep hygiene methods.[24]

Adolescents with CFS experience unrefreshing sleep and sleep disturbances.[2] They have been identified as having significantly longer sleep onset latency, time in bed and total sleep time, later rise time and significantly poorer subjective sleep quality compared with healthy adolescents.[25] There may also be frequent wakenings, day-night reversal and difficulty staying asleep.[2] Education around sleep hygiene is important, in particular avoiding or minimising daytime sleep, while still balancing daytime activity with restful activities to avoid symptom exacerbation from overexertion.

SUGGESTED INITIAL INVESTIGATIONS FOR EVALUATION OF CFS[7]

- Full blood count and differential
- Urea and electrolyte levels
- Calcium, magnesium and phosphate
- C-reactive protein level
- Erythrocyte sedimentation rate
- Blood glucose level
- Thyroid function tests (Free T4 and TSH levels)
- Liver function tests
- Iron studies (serum ferritin level)
- Vitamin D level
- Vitamin B12 and folate levels
- Coeliac serology (tissue transglutaminase, IgA, IgG and serum IgA levels)
- Creatine kinase level
- Urinalysis (blood, glucose)

If refractory symptoms occur after sleep hygiene strategies are in place, the addition of melatonin can be helpful.[2,7]

Mental health conditions

Depression and anxiety are common in adolescents with CFS and may be secondary to the impact of CFS on the young person's life (i.e. reactive); however, we often do not know which came first.[26] A UK study evaluating adolescents who were referred to a specialist CFS unit using structured psychiatric interview found that 38% met the criteria for major depressive disorder, 28% met the criteria for an anxiety disorder and 15% had coexisting anxiety and depression.[27] Australian studies of paediatric CFS diagnosed by paediatricians reported comorbid anxiety and depression in 26% and 13% of cases, respectively.[1] It is important that anxiety, depression and mood disorder are assessed in all adolescents with CFS and appropriate treatment is initiated.[7,27,28]

Somatisation can also complicate the management of CFS. Studies have shown that adolescents with CFS have more somatic complaints than comparison groups of adolescents with other chronic illnesses, and higher somatisation scores on the Children's Somatization Inventory than adolescents with migraine or healthy controls.[29] Somatisation can reinforce illness behaviour and influence illness attribution and needs to be considered in the management of CFS.

Educational impact

Adolescents with CFS have significantly higher rates of school absenteeism, decreased participation, poorer quality of life in the school setting, decreased school connectedness and lower academic performance than healthy adolescents.[30] The high rate of school absenteeism is exacerbated by delays in diagnosis and appropriate management. The average amount of time away from school for students with CFS has been estimated as one year across their school life.[31] Young people with CFS often want to attend school but are prevented from doing so by physical limitations or fear of symptom exacerbation.[2] School refusal is often hard to differentiate from inability to attend school due to symptoms, indicating the importance of a thorough psychosocial assessment. Maintaining engagement in an education system that is flexible and can accommodate the illness and aspirations of adolescents with CFS has been reported as crucial to long-term functioning.[11] Therefore, providing good communication with the school and advocating for the young person to receive flexibility and support at school is essential. This usually involves collaborative decision making between healthcare services, education providers, and the young person and their family around educational options.

Approach to management

The management of children and adolescents with CFS requires an individualised multidisciplinary rehabilitative approach that addresses the biopsychosocial needs of the young person and their family.[32] Recent studies and current clinical practice guidelines recommend that comprehensive management includes:[2,10,29,33,34]

- education and a clear explanation around the condition and complications
- optimising management (pharmacological and nonpharmacological) of troublesome symptoms
- reinforcing sleep regulation
- identifying and managing comorbidities
- encouraging maintenance of social contact and some enjoyable activities
- supporting engagement in education with regular verbal and written school liaison and advocacy.

Individual psychological assessment to elucidate the adolescent's perceptions of their illness and any associated psychological comorbidities, in conjunction with family assessment and support, are important components of CFS management in adolescents.

Referral to a psychologist can be framed as an important step in supporting

PRACTICE POINTS ON CFS

- General practitioners are essential in identifying young people with a history suggestive of chronic fatigue syndrome (CFS) and comorbidities, and referring to other healthcare specialists and allied services when appropriate.
- CFS in adolescents can be associated with significant functional impairment.
- CFS is often associated with medical and psychiatric comorbidities (i.e. orthostatic intolerance, joint hypermobility, sleep disturbance, anxiety or depression) that need to be screened for and managed appropriately.
- Adolescents with CFS require an individualised multidisciplinary rehabilitative approach addressing the biopsychosocial needs of the young person and their family.
- Prognosis in children and adolescents is better that in adults, with recovery expected.

the adolescent to learn how to manage their illness and the often unavoidable and understandable impact it has on their lives and sense of self. Psychological assessment guides the use of a cognitive behavioural therapy framework, which is an evidence-based intervention for CFS that aims to identify and modify unhelpful beliefs and behaviours that may interfere with the adolescent's capacity to actively manage their illness and to increase their understanding of the interaction of biopsychosocial factors in managing symptoms, with the goal to improve level of function and reduce symptom severity.[32,33] Other therapeutic approaches may also be beneficial, with emerging evidence that mindfulness strategies can help to reduce anxiety and stress in adolescents with CFS.[35] Cardiopulmonary exercise testing and consultation with a skilled exercise physiologist can be helpful to guide activity pacing, supported by cognitive behavioural therapy and regular review of progress.[2,3,30,36]

Most adolescents with CFS can be managed within an ambulatory outpatient setting;[2,7] however, adolescents with severe functional impairment are likely to require an inpatient multidisciplinary rehabilitation admission, with a specialised adolescent medicine or chronic fatigue service for further assessment, to manage contributing factors or complications and to allow a more intensive approach to improve level of function and return to school. Ongoing multidisciplinary follow up and educational support as an outpatient can maintain the gains made from an inpatient stay.

Conclusion

CFS in adolescence can be associated with significant functional impairment, as well as medical and psychological comorbidities. However, the prognosis for adolescents with CFS is promising, with recovery expected. General practitioners are essential in identifying children and adolescents with a history suggestive of CFS, undertaking initial assessment and management, providing ongoing support, monitoring progress and ensuring timely referral to a paediatrician or adolescent physician and allied health professionals in order to facilitate optimal outcomes. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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References

1. Knight S, Elders S, Rodda J, et al. Epidemiology of paediatric chronic fatigue syndrome in Australia. Arch Dis Child 2019; 104: 733-738.
2. Rowe PC, Underhill RA, Friedman KJ, et al. Myalgic encephalomyelitis/chronic fatigue syndrome diagnosis and management in young people: a primer. Front Pediatr 2017; 5: 121.
3. Gregorowski A, Simpson J, Segal TY. Child and adolescent chronic fatigue syndrome/myalgic encephalomyelitis: where are we now? Curr Opin Paed 2019; 31: 462-468.
4. Bakken IJ, Tveito K, Gunnes N, et al. Two age peaks in the incidence of chronic fatigue syndrome/myalgic encephalomyelitis: a population based registry study from Norway 2008-2012. BMC Med 2014; 12: 167.
5. Fukuda K, Strauss S, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994; 121: 953-959.
6. Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Board on the Health of Select Populations; Institute of Medicine. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness. Washington, DC: National Academies Press; 2015.
7. National Institute for Health and Care Excellent (NICE). Chronic fatigue syndrome/ myalgic encephalomyelitis (or encephalopathy): diagnosis and management. NICE Clinical Guideline CG53. NICE; 2007.
8. Knight S, Harvey A, Towns S, et al. How is paediatric chronic fatigue syndrome/myalgic encephalomyelitis diagnosed and managed by paediatricians? An Australian Paediatric Research Network Study. J Paediatr Child Health 2014; 50: 1000-1007.
9. Geraghty KJ, Adeniji C. the importance of accurate diagnosis of ME/CFS in children and adolescents: a commentary. Front Pediatr 2018; 6: 435.
10. Klineberg E, Rushworth A, Bibby H, Bennett D, Steinbeck K, Towns S. Adolescent chronic fatigue syndrome and somatoform disorders: a prospective clinical study. J Paediatr Child Health 2014; 50: 775-781.
11. Rowe KS. Long term follow up of young people with chronic fatigue syndrome attending a pediatric outpatient service. Front Pediatr 2019; 7: 21.
12. Rowe K. Paediatric patients with myalgic encephalomyelitis/chronic fatigue syndrome value understanding and help to move on with their lives. Acta Paediatr 2020; 109: 790-800.
13. Holmes GP Kaplan JE, Gantz NM. Chronic fatigue syndrome: a working case definition. Ann Intern Med 1988; 108: 387-389.
14. Carruthers BM, van de Sande MI, De Meirleir KI, et al. Myalgic encephalomyelitis: international consensus criteria. J Intern Med 2011; 270: 327-338.
15. Lim EJ, Son CG. Review of case definitions for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). J Transl Med 2020; 18: 289.
16. Jason LA, Jordan K, Miike T, et al. A pediatric case definition for myalgic encephalomyelitis and chronic fatigue syndrome. J Chronic Fatigue Syndr 2006; 13: 1-44.
17. Garner R, Baraniuk JN. Orthostatic intolerance in chronic fatigue syndrome. J Transl Med 2019; 17: 185.
18. Kizilbash SJ, Ahrens SP, Bruce BK, et al. Adolescent fatigue, POTS, and recovery: a guide for clinicians. Curr Probl Pediatr Adolesc Health Care 2014; 44: 108-133.
19. Stewart JM, Boris JR, Chelimsky G, et al. Pediatric disorders of orthostatic intolerance. Pediatrics 2018; 141: e20171673.
20. Hakim A, De Wandele I, O'Callaghan C, Pocinki A, Rowe P. Chronic fatigue in Ehlers-Danlos syndrome-Hypermobile type. Am J Med Genet C Semin Med Genet 2017; 175: 175-180.
21. Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet 2017; 175: 8-26.
22. The Sydney Children's Hospital (SCHN). Fact sheet: Joint hypermobility 2020. Available online at: https://www.schn.health.nsw.gov.au/fact-sheets/joint-hypermobility (accessed November 2020).
23. Findlay SM. The tired teen: a review of the assessment and management of the adolescent with sleepiness and fatigue. Paediatr Child Health 2008; 13: 37-42.
24. Kotagal S, Pianosi P. Sleep disorders in children and adolescents. BMJ 2006; 332: 828-832.
25. Josev EK, Jackson ML, Bei B, et al. Sleep quality in adolescents with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). J Clin Sleep Med 2017; 13: 1057-1066.
26. Crawley E. Pediatric chronic fatigue syndrome: current perspectives. Pediatric Health Med Ther 2017; 9: 27-33.
27. Loades ME, Rimes KA, Ali S, Lievesley K, Chalder T. The presence of co-morbid mental health problems in a cohort of adolescents with chronic fatigue syndrome. Clin Child Psychol Psychiatry 2018; 23: 398-408.
28. Loades ME, Rimes KA, Ali S, Chalder T. Depressive symptoms in adolescents with chronic fatigue syndrome (CFS): are rates higher than in controls and do depressive symptoms affect outcome? Clin Child Psychol Psychiatry 2019; 24: 580-592.
29. Smith MS, Martin-Herz SP, Womack WM, Marsigan JL. Comparative study of anxiety, depression, somatization, functional disability and illness attribution in adolescents with chronic fatigue or migraine. Pediatrics 2003; 111 (4 Pt 1): e376-e381.
30. Knight SJ, Politis J, Garnham C, Scheinberg A, Tollit MA. School functioning in adolescents with chronic fatigue syndrome. Front Pediatr 2018; 6: 302.
31. Knight S, Harvey A, Lubitz L, et al. Paediatric chronic fatigue syndrome: complex presentations and protracted time to diagnosis. J Paediatr Child Health 2013; 49: 919-924.
32. Knight SJ, Scheinberg A, Harvey AR. Interventions in pediatric chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review. J Adolesc Health 2013; 53: 154-165.
33. Sandler CX, Lloyd AR. Chronic fatigue syndrome: progress and possibilities. Med J Aust 2020; 212: 428-433.
34. Rowe KS, Apple A, McDonald F. Self management of chronic fatigue syndrome in adolescents. InTech Open 2020. Available online at: https://www.intechopen.com/online-first/self-management-of-chronic-fatigue-syndrome-in-adolescents (accessed November 2020).
35. Ali A, Weiss TR, Dutton A, et al. Mindfulness-based stress reduction for adolescents with functional somatic syndromes: a pilot cohort study. J Pediatr 2017; 183: 184-190.
36. Working Group of the Royal Australasian College of Physicians. Chronic fatigue syndrome - clinical practice guidelines - 2002. Med J Aust 2002; 176(S9): S17-S55.