

Aerobic capacity and muscle strength in juvenile-onset mixed connective tissue disease (MCTD)

J van der Net¹, B Wissink², A van Royen³, PJM Helders¹, T Takken¹

¹Child Development and Exercise Centre, Wilhelmina Children's Hospital, University Medical Centre Utrecht, ²University College Utrecht, Utrecht University, and ³Department of Paediatric Immunology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, The Netherlands

Objectives: To study the aerobic capacity and muscle strength in children and adolescents with mixed connective tissue disease (MCTD). Frequently reported clinical symptoms include joint swelling, muscle weakness, fatigue, decreased stamina/exercise tolerance, and shortness of breath. The exercise capacity of patients with MCTD has not been studied systematically in this detail before.

Methods: Eleven children and adolescents diagnosed with MCTD (mean age 15.7 years, range 11.3–19.9 years) were studied. Maximal exercise testing on a cycle ergometer was used to determine the peak oxygen uptake (VO_{2peak}) and a hand-held dynamometer was used to measure muscle strength. Cardiac and pulmonary function tests (ultrasonography, electrocardiography, spirometry) were used to measure cardiac function and obstructive or restrictive respiratory impairment. Complementary data (e.g. disease duration and concurrent symptoms) were collected from a medical chart review.

Results: VO_{2peak} was significantly lower in patients with MCTD compared to the VO_{2peak} of healthy subjects (Z-score -1.9 , $p = 0.008$). The strength of the proximal muscles (hip flexors, shoulder abductors, knee extensors) of the patients was significantly lower than in the controls, whereas the strength of the distal muscles (dorsal flexors of the foot and handgrip strength) showed no differences. In eight children, arthritis was observed. No clinically relevant impairment in cardiac or pulmonary function was observed.

Conclusions: Aerobic capacity and also proximal muscle strength were significantly impaired in our sample of children and adolescents with MCTD. Because respiratory problems were non-dominant in our patient group, the decreased aerobic capacity and muscle strength were probably caused by musculoskeletal impairments. Further studies in larger multicentre samples are warranted to confirm our findings.

Mixed connective tissue disease (MCTD) was recognized as a distinct disease in adults by Sharp et al in 1972 (1). The clinical symptoms are closely related to those of other well-known autoimmune diseases such as systemic lupus erythematosus, scleroderma, and polymyositis, and include Raynaud's phenomenon, polyarthritis, myositis, and cardiopulmonary impairment. To further distinguish MCTD patients, laboratory tests revealing the presence of antibodies against U1 small nuclear ribonucleoproteins (U1snRNP) have been strongly recommended (2). Kasukawa et al (3) include the presence of U1snRNP as a criterion for the diagnosis of MCTD. This criterion, however, is not conclusive for MCTD because patients with clinical features of MCTD features may lack the presence of U1snRNP (4).

To date, there is no international consensus on the criteria for diagnosing MCTD.

Clinical observations are consistent in describing musculoskeletal impairments in MCTD patients (2, 4). In some childhood rheumatic diseases, such as juvenile idiopathic arthritis (JIA) and juvenile dermatomyositis (JDM), musculoskeletal impairment and its consequences for physical fitness have been studied in some detail (5–8) whereas studies on musculoskeletal impairment (e.g. exercise capacity and muscle strength) in children with MCTD are scarce. In 1993 we reported that muscle weakness, decreased exercise tolerance, and impaired pulmonary function were prominent in 40, 30, and 50%, respectively, of a patient sample with MCTD (4), but aerobic capacity was not measured in that study. Treatment of paediatric rheumatic disease has advanced in the past two decades, and children are currently advised to remain physically active during treatment.

The aim of the current study was therefore to investigate the aerobic capacity as well as the muscle strength in contemporary children with MCTD.

Tim Takken, Child Development and Exercise Centre, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Room KB.02.056, PO Box 85090, 3508 AB, Utrecht, The Netherlands.
E-mail: t.takken@umcutrecht.nl

Accepted 2 March 2010

Patients and methods

Patient population

Children and adolescents who had been diagnosed with MCTD and are being treated in a tertiary university centre for paediatric rheumatic diseases were included in the study. Maximal exercise tests, muscle strength tests, and anthropometric measures needed for interpretation of the results were performed between April 2004 and November 2006 during one visit. Cardiac and pulmonary function tests were performed at the same visit or within 6 months of the test date. If the patients' history or the results of the cardiac and pulmonary function tests contraindicated a maximum exercise test, these children were excluded from the study. All study procedures were approved by the Medical Ethics Committee of the University Medical Centre Utrecht.

Anthropometrical measurements

The patients' body weight and height were measured using an electronic scale and a wall-assembled stadiometer. Both weight and height were determined without wearing shoes and heavy clothing, to the nearest 100 g and centimetre, respectively. Body mass index (BMI) was calculated by dividing the weight of the patients by the square of the height in metres. Z-scores were calculated for weight for age, height for age, and BMI for age from Dutch growth charts using the Growth Analyzer software package (Growth Analyzer 3.5, Dutch Growth Foundation, Rotterdam, The Netherlands).

Cardiopulmonary function tests

History of previous cardiac or pulmonary disease (ultrasonography, electrocardiography, pulmonary function test results) was obtained from the patients' medical charts.

Maximal exercise test

The maximal exercise test was performed using an electronically braked cycle ergometer (Lode Examiner, Lode BV, Groningen, The Netherlands). The seat of the ergometer was adjusted to the patient's leg length. The test started with 1 min of unloaded cycling. After this, the work rate was increased by 20 W/min. This protocol continued until the patient stopped because of voluntary exhaustion, despite verbal encouragement from the test leader. This protocol ensures that the test lasts about 6 to 12 min (9). Peak work rate (W_{peak}) was taken as the work rate during the last completed exercise stage.

During the maximal exercise test, the subject breathed through a facemask (Hans Rudolph Inc, Kansas City, MO, USA) connected to a calibrated metabolic cart (Oxygon Pro, Jaeger, Viasys, Care Fusion, Houten, The

Netherlands). Expired gas passed through a flowmeter (Triple-V volume transducer), an oxygen analyser and a carbon dioxide analyser. The flowmeter and gas analysers were connected to a computer that calculated breath-by-breath minute ventilation (VE), oxygen uptake (VO_2), carbon dioxide production (VCO_2), and the respiratory exchange ratio ($RER = VCO_2/VO_2$) from conventional equations. Heart rate (HR) was measured continuously throughout the maximal exercise test using a bipolar electrocardiogram. Transcutaneous oxygen saturation ($SpO_2\%$) was measured by pulse oximetry at the index finger or ear lobe (Nellcor 200 E, Breda, The Netherlands).

Maximal effort was defined when either the RER was >1.0 or when the HR had reached >180 beats/min, which has been shown to be the lower limit of normal in healthy children (10). Breathing reserve was calculated as maximal voluntary ventilation [forced expiratory volume in 1 s (FEV1) \times 40] minus VE_{peak} (11); in addition, the dyspnoea index was calculated as $VE_{\text{peak}}/\text{mandatory minute ventilation (MVV)}$. Cut-off points for breathing reserve and the dyspnoea index are 15 L/min and 30%, respectively (12).

$VO_{2\text{peak}}$ and other exercise variables were calculated as the average of the values measured in the last 30 s of the test. To correct for body proportion, the $VO_{2\text{peak}}$ per kilogram ($VO_{2\text{peak/kg}}$) was calculated. All tests were performed and analysed by a medical physiologist (TT), who also documented the limiting symptom at the moment the patient voluntarily stopped exercising. Reference values for the maximal exercise tests of a sample of healthy Dutch children were obtained from Binkhorst et al (13).

Muscle strength test

Muscle strength was measured as muscle force (in newtons, N) using a hand-held dynamometer (Citec dynamometer CT 3001, C.I.T. Technics, Groningen, The Netherlands) (14). Maximal isometric muscle strength was tested by means of the 'break' method. In this method, the examiner gradually overcomes the muscle strength of the patient and stops at the moment the extremity gives way (15). The instrument is placed between the examiner's hands and the extremity of the patient to read the muscle force in newtons. The dynamometer position on the extremity was according to the measurement protocol of Beenakker et al (15). To test for proximal as well as distal muscle strength in both the upper and lower extremities, the following muscle groups were measured: shoulder abductors, hip flexors, knee extensors, dorsal flexors of the foot, wrist extensors, and grip strength. Measurements were carried out three times on both the left and right muscle groups and the location of the dynamometer was secured in each measurement according to the Beenakker protocol (15). The average of the highest values (in newtons) of both sides was calculated and this value was used for

analysis. Reference values were acquired from a sample of healthy Dutch children published by Beenakker et al (15), with the exception of 'grip strength', which was based on reference values published by Wind et al (16). All muscle strength tests were performed by an experienced paediatric physiotherapist (JN). Between muscle strength testing and maximal exercise testing, a rest period of 45 min enabled the muscles to recover from local fatigue.

Statistical analysis

SPSS for Windows version 12.0 (SPSS Inc, Chicago, IL, USA) was used for analysis of the results. The data from the exercise test and muscle strength tests were transformed into Z-scores to allow for comparison with reference values. Z-scores were calculated using the difference between the score of each individual patient and the reference values for age and gender, divided by the standard deviation of the reference values. A Z-score indicates how many standard deviations an observation is above or below the mean. Normal scores for Z-scores are between -2 and +2. Descriptive statistics were used to present all outcomes as means with standard deviation (\pm SD). Independent t-tests were used to compare the results of the patients with MCTD with the reference values. The significance level was set at 0.05.

Results

Eleven children and adolescents (eight girls, three boys) diagnosed with MCTD were included in the study. Their mean age was 15.7 ± 2.4 (range 11.3–19.9) years, and the mean duration of disease was 0.96 ± 0.95 (range 0.0–2.7) years. The subjects had a normal weight, height and BMI for age. None of the patients were obese.

According to the review of their medical charts, all of the children were classified according to Kasukawa's criteria and eight were found to have autoantibodies against U1snRNP. Ten patients were on medication at the time of the test: five of the 11 patients were taking methotrexate (MTX); four of 11 patients were on prednisone maintenance therapy; other medication included non-steroidal anti-inflammatory drugs and hydroxychloroquine. None

Table 1. Demographic and clinical data for 11 children with MCTD.

Age	15.7 \pm 2.4 (11.3–19.9)
Weight (kg)	53.8 \pm 9.8 (40.7–70.5)
Weight for age (Z-score)	-0.269 \pm 1.13 (-2.39 to 1.06)
Height (cm)	165.3 \pm 10.2 (150.5–179.2)
Height for age (Z-score)	-0.34 \pm 1.07 (-2.2 to 1.66)
BMI (kg/m ²)	20.14 \pm 3.33(16.4–26.5)
BMI for age (Z-score)	-0.13 \pm 1.3 (-2.3 to 1.62)
Musculoskeletal disease	
Arthritis	8
Myositis	7
Cardiopulmonary disease	
Obstructive lung disease	2 (reversible)
Restrictive lung disease	6 (mild)
Cardiac arrhythmias	1 (previously)

Values given as mean \pm SD (range) or number.

of the patients had been treated with cyclophosphamide. One patient was not on medication at the time of the study but had been on MTX and prednisone previously (medication-free interval <6 months). Table 1 summarizes the patient characteristics.

Pulmonary function tests (spirometry) showed a mean FEV1 of $88.6 \pm 16.7\%$ (range 52–121%) of predicted. Based on the reports in the patient charts, in the case of pulmonary restriction, high-resolution computed tomography (CT) scans did not lead to any alteration of the medication regime.

There were no contraindications to perform the maximal exercise test in all 11 children. All tests were performed uneventfully. Table 2 shows the outcome of the several variables of the maximal exercise test. RER_{peak} of the patients was 1.3 ± 0.2 (range 1.1–1.7). Together with the $HR_{peak} > 180$, this indicates that our patients gave a maximal effort. There was no significant reduction in $SpO_2\%$ during exercise (all patients remained above 96%). The mean of the Z-scores for VO_{2peak} was -1.9 ($p = 0.008$). The mean of the Z-score for $VO_{2peak/kg}$ was also significantly lower than the reference values (-2.7, $p = 0.001$). Similar results were found for HR_{peak}

Table 2. Comparison of parameters of exercise capacity of children with MCTD to reference values (n = 11).

Parameter	MCTD patients Mean \pm SD (range)	Z-score Mean \pm SD	Reference values Mean \pm SD (range)	p-value
VO_{2peak} (mL/min)	1529.9 \pm 607.2 (584.0–2483.0)	-1.9 \pm 1.0	2209.1 \pm 427.5 (1600–3200)	0.008
$VO_{2peak/kg}$ (mL/min/kg)	28.1 \pm 10.9 (13.7–45.6)	-2.7 \pm 1.6	41.5 \pm 4.7 (38.0–50.8)	0.001
HR_{peak} (beats/min)	177.1 \pm 17.6 (146.0–199.0)	-2.1 \pm 2.3	193.0 \pm 0.3 (192.2–193.4)	0.007
W_{peak} (W)	138.8 \pm 57.4 (66.7–240.0)	-2.8 \pm 1.2	213.7 \pm 38.5 (160.1–292.9)	0.002
VE_{peak} (L/min)	54.2 \pm 24.9 (27.0–98.8)	-1.5 \pm 0.9	75.9 \pm 16.3 (55.3–107.5)	0.033

VO_{2peak} , peak oxygen uptake; $VO_{2peak/kg}$, peak oxygen uptake per kilogram body mass; HR_{peak} , peak heart rate; W_{peak} , peak work rate; VE_{peak} , peak ventilation.

Table 3. Comparison of muscle strength of children with MCTD to reference values (in newtons).

Muscle group	MCTD patients Mean \pm SD (range)	Z-score Mean \pm SD	Reference values Mean \pm SD (range)	p-value
Shoulder abductors	89.7 \pm 38.5 (44–144)	-2.5 \pm 1.7	161.2 \pm 34.4 (110–219)	0.001
Hip flexors	131.3 \pm 60.8 (60–233)	-3.0 \pm 1.2	280.8 \pm 27.4 (232–301)	0.000
Knee extensors	230.7 \pm 112.0 (85–450)	-1.4 \pm 1.1	320.9 \pm 60.3 (239–373)	0.049
Dorsal flexors of foot	193.7 \pm 75.8 (110–275)	-0.9 \pm 1.8	211.8 \pm 37.1 (149–232)	0.530
Wrist extensors	89.4 \pm 64.1 (31.5–219)	-4.1 \pm 5.9	144.1 \pm 35.6 (100–218)	0.053
Grip strength	106.1 \pm 63.4 (37.5–227)	0.5 \pm 3.3	91.9 \pm 17.1 (70–106)	0.549

(Z-score -2.1, $p = 0.007$), W_{peak} (Z-score -2.8, $p = 0.002$) and VE_{peak} (Z-score -1.5, $p = 0.033$). In total, 72% of the patients had a Z-score lower than -2 with regard to the $VO_{2\text{peak}}$. Although several children had restricted pulmonary function at rest, none of the patients showed a pulmonary limitation during exercise (mean breathing reserve: 59.9 ± 24 L/min), and none of the patients had a breathing reserve below 15 L/min or a dyspnoea index below 30%.

The results on muscle testing are presented in Table 3. The data from two tests were lost due to technical failure of the hand-held dynamometer and in one visit the results for wrist extensors and grip strength were lost for analysis. Five out of the six muscle groups tested scored below the mean of the reference. Of these five, the Z-scores of the shoulder abductors, the hip flexors and the knee flexors were significantly lower than the reference values (shoulder abductors: Z-score -2.5, $p = 0.001$; hip flexors: Z-score -3.0, $p = 0.000$; knee flexors: Z-score -1.4, $p = 0.49$). The muscle strength of the dorsal flexors and wrist extensors also decreased, but not significantly (dorsal flexors: Z-score -0.9, $p = 0.530$; wrist extensors: Z-score -4.1, $p = 0.053$). The grip strength was slightly higher than the reference values (Z-score 0.5, $p = 0.549$). The patients scored worst on the proximal muscles of the hip and shoulder, which is compatible with the proximal myositis in MCTD. Seventy-eight per cent had a Z-score of lower than -2 for the muscle strength of the hip and 67% had a Z-score of lower than -2 for the muscle strength of the shoulder muscles.

We performed a power calculation for the most important outcomes. With an alpha of 0.05, this study had a power of 0.9 with the sample size of 11 patients to detect a significant difference in $VO_{2\text{peak/kg}}$ between patients and reference values. This shows that this study was sufficiently powered for detecting differences in $VO_{2\text{peak/kg}}$ (power > 0.8). With an alpha of 0.05, this study had a power of 0.9 with the sample size of 11 patients to detect a significant difference in knee extensor strength between patients and reference values. This shows that this study was sufficiently powered for detecting significant differences in knee extensor muscle strength (power > 0.8). In addition, for shoulder abductors and hip flexors this study was sufficiently

powered to detect a significant difference between patients and reference values with the current sample size (power > 0.8).

Discussion

The aim of this study was to study the aerobic capacity and muscle strength in children and adolescents with MCTD. The results show that the aerobic capacity of patients with MCTD was significantly impaired on all exercise parameters measured in comparison to healthy subjects. Muscle weakness was most prominent in the proximal muscle groups.

Despite the reported restrictive pulmonary function tests in the patient charts, we found no clinically relevant cardiac or pulmonary impairment that could have affected the outcome on the aerobic capacity. As there were no alterations in the medication regime, we concluded that the restriction found had to be relatively mild. In addition, there was no pulmonary limitation during exercise. These observations are in line with a recent study in 24 patients with MCTD that reported that the pulmonary abnormalities in MCTD are subtle and without clinical correlation (17).

Although all patients with MCTD were considered to have problems in the musculoskeletal and/or cardiac or pulmonary system beforehand, we found no contraindications and exercise testing was performed without complications. Under these conditions, the maximal exercise test used in this study can therefore be regarded a safe test for children and adolescents with MCTD. This finding is concordant with our findings in other childhood rheumatic diseases (18, 19).

The aerobic capacity of patients with other childhood rheumatic diseases has been studied before. Takken et al (18) reported the aerobic capacity of children with JDM and found that their exercise capacity was considerably reduced, with a mean Z-score of -1.82 for $VO_{2\text{peak}}$ and a mean Z-score of -2.83 for $VO_{2\text{peak/kg}}$. These results are very similar to the current results in MCTD patients. Furthermore, Van Brussel et al (19), Metin et al (20), and Lelieveld et al (21) studied the exercise capacity of children and adolescents with JIA and reported a reduction of 69.8% in children with JIA (19)

and 82% in adolescents with JIA (21), respectively, which is similar to our findings in childhood MCTD.

The results for muscle strength in our patients show that muscle function of the proximal muscle groups was significantly impaired, whereas the strength of the distal muscles did not differ significantly from the muscle strength measured in healthy subjects. The clinical pattern of proximal muscles being more affected than distal muscles in patients with MCTD was reported previously in 1995 (22). This pattern is very similar to the clinical pattern that has been described in JDM or juvenile polymyositis (JPM) (23). This similarity between juvenile MCTD and JDM or JPM underlines the overlap character of MCTD within the spectrum of childhood rheumatic diseases. The pattern of proximal weakness might very well be one of the causal factors for the exercise limitation that was found in our patient group, in particular because the test used in this study is a bicycle ergometer test that primarily challenges the proximal muscles of the lower extremities. Additionally, about 35% of our patient group were on corticosteroids, which can induce muscle weakness and may also contribute to exercise limitation (21).

These reductions in aerobic capacity and muscle strength indicate that exercise therapy might be indicated for this patient group (24). Future controlled studies investigating the effects of exercise therapy seems warranted.

The choice for measuring muscle strength instead of muscle torque in this study is based on the availability of Dutch reference values [from Beenakker et al (15)], the extensive experience in using a dynamometer and Beenakker's methodology for evaluation of muscle function at our department. It is important to recognize that this will limit comparison with other studies as muscle force measures are influenced by individual body proportions where muscle torques are adjusted for this potential bias. However, to our knowledge, reference values for muscle strength measured in torques using the hand-held dynamometer are not available.

A possible confounder is the age range of our patient group (11–19 years), which exceeds the age range of the reference group (4–16 years) of the study of Beenakker et al (15). The impact of this limitation is small, as we tested only one female person above the age of 16 years. There is little increase in muscle strength after the age of 16 years in females (16). Further limitations of this study are the small patient sample from a single centre. However, the findings in this limited patient sample and its clinical relevance underline the need for future studies in larger, multicentre samples. These studies are warranted to confirm our findings. The feasibility of safe exercise testing in juvenile MCTD opens up the way to proceed in this direction.

In conclusion, this study found that the aerobic capacity and the workload are significantly reduced

in children and adolescents with MCTD. This is probably caused by impairment of the musculoskeletal system rather than by cardiac or pulmonary impairment. The levels of reduction of aerobic capacity are similar to those in patients with JDM and JIA. Furthermore, the muscle strength of the proximal muscles of the patients was reduced compared to the healthy controls.

References

1. Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease – an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). *Am J Med* 1972;52:148–59.
2. Hoffman RW, Greidinger EL. Mixed connective tissue disease. *Curr Opin Rheumatol* 2000;12:386–90.
3. Kasukawa R, Tojo T, Miyawaki S. Preliminary diagnostic criteria for classification of mixed connective tissue disease. In: Kasukawa R, Sharp GC, editors. *Mixed connective tissue disease and anti-nuclear antibodies*. Amsterdam: Excerpta Medica, 1987:41–7.
4. Tiddens HA, van der Net JJ, de Graeff-Meeder ER, Fiselier TJW, de Rooij DJ, van Luijk WHJ, et al. Juvenile onset mixed connective tissue disease: longitudinal follow-up. *J Pediatr* 1993;122:191–7.
5. Lindehammar H, Backman E. Muscle function in juvenile chronic arthritis. *J Rheumatol* 1995;22:1159–65.
6. Lindehammar H, Sandstedt P. Measurement of quadriceps muscle strength and bulk in juvenile chronic arthritis. A prospective, longitudinal, 2-year survey. *J Rheumatol* 1998;25:2240–8.
7. Hedengren E, Knutson LM, Haglund-Akerlind Y, Hagelberg S. Lower extremity isometric joint torque in children with juvenile chronic arthritis. *Scand J Rheumatol* 2001;30:69–76.
8. Klepper SE. Exercise in paediatric rheumatic disease. *Curr Opin Rheumatol* 2008;20:619–24.
9. Hebestreit H. Exercise testing in children – what works, what doesn't, and where to go to? *Ped Respir Rev* 2004;5:S11–14.
10. Schulze-Neick IM, Wessel HU, Paul MH. Heart rate and oxygen uptake response to exercise in children with low peak exercise heart rate. *Eur J Pediatr* 1992;151:160–6.
11. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. *Principles of exercise testing and interpretation*, 3rd edn. Baltimore, MD: Lippincott, Williams & Wilkins, 1999.
12. Eschenbacher WL, Mannina A. An algorithm for the interpretation of cardiopulmonary exercise tests. *Chest* 1990;97:263–7.
13. Binkhorst RA, van 't Hof MA, Saris WHM. [Maximal exercise in children; reference values girls and boys, 6–18 year of age], in Dutch. Den-Haag: Nederlandse Hartstichting, 1992.
14. Van der Ploeg RJO, Oosterhuis HJGH, Reuvekamp J. Measuring muscle strength. *J Neurol* 1984;231:200–3.
15. Beenakker EAC, van der Hoeven JH, Fock JM, Maurits NM. Reference values of maximum isometric muscle force obtained in children aged 4–16 years by hand-held dynamometry. *Neuromus Dis* 2001;11:441–6.
16. Wind AE, Takken T, Helders PJ, Engelbert RH. Is grip strength a predictor for total muscle strength in healthy children, adolescents, and young adults? *Eur J Pediatr* 2010;169:281–7.
17. Aalokken TM, Lilleby V, Soyseth V, Mynarek G, Pripp AH, Johansen B, et al. Chest abnormalities in juvenile-onset mixed connective tissue disease: assessment with high resolution computed tomography and pulmonary function tests. *Acta Radiol* 2009;50:430–6.
18. Takken T, Spermon N, Helders PJM, Prakken ABJ, van der Net J. Aerobic exercise capacity in patients with juvenile dermatomyositis. *J Rheumatol* 2003;30:1075–80.

19. van Brussel M, Lelieveld OT, van der Net J, Engelbert RHH, Helders PJM, Takken T. Aerobic and anaerobic exercise capacity in children with juvenile idiopathic arthritis. *Arthritis Rheum* 2007;57:891–7.
20. Metin G, Oztürk L, Kasapcopur O, Apelyan M, Arisoy N. Cardiopulmonary exercise testing in juvenile idiopathic arthritis. *J Rheum* 2004;31:1834–9.
21. Lelieveld OT, van Brussel M, Takken T, van Weert E, van Leeuwen MA, Armbrust W. Aerobic and anaerobic exercise capacity in adolescents with juvenile idiopathic arthritis. *Arthritis Rheum* 2007;57:898–904.
22. van der Net J, van der Hoeven H, Esseveld F, Wilde EJ, Kuis W, Helders PJM. Musculoskeletal disorders in juvenile onset mixed connective tissue disease. *J Rheumatol* 1995;22:751–7.
23. Cassidy JT, Petty RE. Textbook of pediatric rheumatology, 4th edn. Philadelphia, PA: W.B. Saunders Company, 2001.
24. Takken T, van Brussel M, Engelbert RH, van der Net J, Kuis W, Helders PJ. Exercise therapy in juvenile idiopathic arthritis: a Cochrane Review. *Eur J Phys Rehabil Med* 2008; 44:287–97.