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SPORADIC INCLUSION BODY MYOSITIS: PILOT STUDY ON THE EFFECTS OF A HOME EXERCISE PROGRAM ON MUSCLE FUNCTION, HISTOPATHOLOGY AND INFLAMMATORY REACTION

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***Objective*: To evaluate the safety and effect of a home training program on muscle function in 7 patients with sporadic inclusion body myositis.**

***Design*: The patients performed exercise 5 days a week over a 12-week period.**

***Methods*: Safety was assessed by clinical examination, repeated muscle biopsies and serum levels of creatine kinase. Muscle strength was evaluated by clinical examination, dynamic dynamometer and by a functional index in myositis.**

***Results*: Strength was not significantly improved after the exercise, however none of the patients deteriorated concerning muscle function. The histopathology was unchanged and there were no signs of increased muscle inflammation or of expression of cytokines and adhesion molecules in the muscle biopsies. Creatine kinase levels were unchanged. A significant decrease was found in the areas that were positively stained for EN-4 (a marker for endothelial cells) in the muscle biopsies after training.**

***Conclusion*: The home exercise program was considered as not harmful to the muscles regarding muscle inflammation and function. Exercise may prevent loss of muscle strength due to disease and/or inactivity.**

Key words: s-IBM, exercise program, muscle function, muscle inflammation, cytokines, adhesion molecules.

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INTRODUCTION

Sporadic inclusion body myositis (s-IBM) is an acquired slowly progressive inflammatory myopathy (1) and is most common among males over 50 years of age (2, 3). The typical clinical findings are proximal weakness and atrophy in the lower extremities, most prominent in the quadriceps muscles, and distal weakness and atrophy in the arms, most prominent in the wrist and finger flexors (4). Serum creatine kinase (CK) is normal or moderately elevated, less than 12 times normal (2, 4).

Light microscopical abnormalities on muscle biopsy include inflammation with mononuclear inflammatory cells, mainly CD8+ T cells and macrophages and rimmed vacuoles in muscle fibres (5). The functional role of the inflammatory cells in the inflamed muscle tissue is uncertain. The products of the inflammatory cells, such as cytokines, have important functions in inflammatory processes as both up-regulating and down-regulating factors. In idiopathic inflammatory myopathies, such as s-IBM, the pro-inflammatory cytokines interleukin-1α (IL-1α), interleukin H1 (IL-1β) and tumour necrosis factor (TNF-α), which are mainly produced by monocytes and macrophages, predominate in muscle tissue (6). Interleukin-1 can induce up-regulation of adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and vascular cellular adhesion molecule 1 (VCAM-1), they are important in the homing process of inflammatory cells to the tissue (6).

There is no effective treatment for the disease. Previously, physical training has not been recommended for patients with inflammatory myopathies, due to the notion that physical activity could increase the inflammatory process in the muscle (7, 8). However, Wiesinger et al. (9, 10) showed that physical training of patients with polymyositis (PM) and dermatomyositis (DM) resulted in muscle strength improvement without increase in inflammatory reaction. Alexanderson et al. (11) evaluated the safety and effects of a home exercise program in patients with stable, inactive PM and DM. They concluded that the program could be used safely, with beneficial effects on muscle function. There is one previous study published on the effect of exercise in IBM patients (12). In that study the effects of a 12-week strength-training program in patients with IBM were analysed and it was concluded that training could lead to gain in strength without causing muscle injury in this subgroup of myositis (12).

The aim of this study was to evaluate the safety and effects on disease activity and muscle strength of a home exercise program in s-IBM patients, using a program with the same design as was earlier found to be safe and beneficial in patients with PM and DM (11) and analyse the muscle fibre and inflammatory changes after exercise using muscle biopsies taken before and after exercise. The muscle fibre morphological and morphometric changes based on histopathology and fibre type were analysed. The inflammatory reaction was analysed by evaluating the T-cells, macrophages, pro-inflammatory cytokines such as IL-1α and IL-1β, cytokine inhibitor interleukin-1 receptor antagonist (IL-1Ra) and adhesion molecules such as ICAM-1 and VCAM-1.

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Table I. *Clinical data, creatine kinase (CK) values and outcome of Medical Research Council scale (MRC) grades and functional index in Myositis (FI) in the sporadic-inclusion body myositis (s-IBM) patients at baseline (12 weeks before training), immediately before and after the home exercise program*

			Serum CK (IU/l)			MRC grades			FI index		
Case (age in years)	Years from diagnosis	Therapy	Baseline	Pre-training	Post-training	Baseline	Pre-training	Post-training	Baseline	Pre-training	Post-training
1. M/78	6	IVIg	408	372	222	87	77	91	21.0	18	18.5
2. M/72	4	IVIg	270	258	276	116	108	110	34.5	32.0	32.0
3. M/65	2	IVIg	198	60	144	122	118	118	45.0	46.0	45.0
4. M/63	2	IVIg	228	462	384	120	114	114	37.5	37.5	34.5
5. M/52	3	IVIg	1182	1446	1290	98	104	101	45.0	38.0	45.0
6. M/48	2	Pred	282	264	408	133	135	137	58.0	60.0	62.5
7. M/45	2	IVIg	384	360	438	109*	106*	109*	13.5	14.5	17.0

M = male. IVIg = intravenous immunoglobulin. Pred = prednisolone. CK normal value <198 IU/l. MRC max 140. FI max 64 a mean value of right and left side. * Missing data, hip flexors max. MRC 130.

MATERIAL AND METHODS

Patients

Seven men, in the age range 45–78 years (mean age 60.4 years), with s-IBM participated in the study (Table I). The diagnosis was based on clinical symptoms and signs as well as histopathological changes in muscle biopsy, using the diagnostic criteria for s-IBM according to Griggs et al. (4). The mean duration from the diagnosis was 3 years (range 2–6 years). Six of the patients were treated with intravenous immunoglobulin (IVIg) 30 g/daily/3 days every 8 weeks from 9 months to 3 years and 1 patient was treated with prednisolone 25 mg/day for 1 year. No changes in medication were made during the baseline and study period.

The study was approved by the local ethics committee of the Karolinska Hospital.

Study design

Clinical examination, laboratory and muscle strength assessments were conducted before a 3-month baseline period, immediately before and after 12 weeks of training, by 1 physician (SA) and 1 physiotherapist (HA).

Muscle biopsy was performed before and after the training period. Serum levels of CK were measured at baseline, immediately before and after 12 weeks of training. Muscle strength was evaluated by clinical examination, dynamic dynamometer and assessed with a functional index (FI) according to Josefson et al. (13).

Strength measurement. Clinical examination of muscle strength, the manual muscle test (MMT), was made by the same neurologist, using the Medical Research Council (MRC) scale (14), 5-degree scale, in neck flexors and extensors and in the following muscles bilaterally: shoulder abductors, elbow flexors and extensors, wrist flexors and extensors, finger flexors and extensors, hip flexors, knee flexors and extensors, foot plantar flexors and dorsal flexors and extensor hallucis longus. The maximum possible total sum of score was 140.

Maximal voluntary knee extension and flexion were measured in isokinetic, concentric, movements with dynamic dynamometer (KIN-COM 500, Chattex Corp., Chattanooga, TN) at angular velocity 120°/s and peak torque values were determined in 4 of the 7 patients. The best of 3 trials was recorded.

Functional index

Muscle function was assessed and scored with the "functional index in myositis" (FI) as earlier described (13). Total score of the FI is 64 for right and left sides respectively, which indicates normal muscle function. The FI sets out to measure function in the upper and lower limbs as well as ability to transfer sideways when lying down and in a sitting position and finally peak expiratory flow (PEF). The FI was modified, as the Grippit instrument (15) was used for measuring grip strength instead of the sphygmomanometer originally used (13).

Training program. Each patient was individually trained to perform a standardized 15-minute home exercise program and to take a 15-minute self paced walk 5 days a week over a period of 12 weeks (11). The exercise program was divided into a moderate and an easy program. Patients with FI score >38 were given the moderate program and the resistance was individually adjusted with weight cuffs of 0.25–2 kg. The moderate program included exercises for shoulder mobility with a pulley apparatus, resistive exercises for shoulder muscles, hip muscles, quadriceps and neck and trunk muscles. The easy program did not include resistive exercises for shoulder muscles and had modified easier resistive exercises for hip muscles not using any weight cuffs. In the end of both programs careful stretching of the neck muscles, quadriceps, hamstrings, trunk and shoulder muscles was performed. The programs included 10 repeats of each exercise.

Along with the exercise program the patients were given tape-recorded instructions with music and were also instructed to write an exercise diary. The same physiotherapist, who also contacted the patients by telephone once a week during the 12-week exercise period, instructed all patients.

Muscle biopsy

Muscle biopsy was performed in 6 of the 7 patients, in m. vastus lateralis (VL) in 5 patients and m. tibialis anterior (TA) in 1 patient, using the percutaneous conchotome method (16). One of the patients refused repeated muscle biopsy. Muscle biopsies from 2 men with no muscle disease were used as controls, 1 from TA and 1 from VL.

The biopsy material obtained was immediately frozen in Freon 22, which was kept at its melting point (−190°C) by liquid nitrogen, and then placed in a freezer at −75°C until further processed. Sections of 10–15 μm were cut in a cryostat operating at −25°C.

Histopathology. Cross-sections were stained with haematoxylin-eosin (HTX) for routine histopathology and for myofibrillar ATPase (mATPase) and classified as type I and type II A, II B and II C (17, 18). The histopathological findings in the muscle biopsies were graded and defined as: 0 = normal muscle; + = mild changes, increased variability in muscle fibre sizes, internal nucleation, slight degenerative and regenerative changes; ++ = moderate changes, prominent degenerative and regenerative changes; +++ = moderate to severe changes, slight fibrosis and fatty infiltration; ++++ = severe changes, no fibres of normal size, fibrosis and fatty infiltration; * = end stage muscle, mostly fibrosis and fat, few scattered atrophic muscle fibres.

The cross-sectional area of the muscle fibres stained with mATPase was measured directly from the microscope via a CCD camera (Hamamatsu C3077, Hamamatsu Photonics KK, Japan) connected to an image-analysis processor (VIDAS, Kontron Bildanalyse, GmbH, Munich, Germany).

Immunohistochemistry. In addition to traditionally histopathological evaluation, T-lymphocytes, macrophages, endothelial cells, cytokines

Table II. *Histopathological changes, morphology and morphometry in the muscle biopsies before and after the training*

Patient and biopsy	Muscle	Histopathology grade	Mean type I fibre cross-sectional area μm^2 (SD)	Mean type II a + b fibre cross-sectional area μm^2 (SD)	Type I %	Type IIa %	Type IIb %	Type IIc %
1. I	VL	++++	2985 (1980)	783 (540)	75	1	9	15
II	VL	*	ND	ND	ND	ND	ND	ND
2. I	VL	+++	2480 (2162)	1085 (1108)	33	23	31	13
II	VL	*	ND	ND	ND	ND	ND	ND
3. I	VL	++++	1198 (855)	915 (502)	47	0	33	20
II	VL	++++	1964 (1982)	920 (598)	56	6	14	24
5. I	TA	++++	1277 (1109)	1149 (991)	60	12	19	9
II	TA	+++	1928 (2893)	895 (477)	57	4	14	25
6. I	VL	+	8643 (2410)	6859 (2420)	21	32	46	1
II	VL	+	10036 (4121)	8041 (3183)	9	32	53	6
7. I	VL	++	7801 (3228)	6249 (2478)	37	34	26	3
II	VL	++	8236 (2733)	5969 (2524)	38	34	21	7
Co.	VL	0	5652 (1548)	6261 (1759)	40	25	34	1
Co.	TA	0	5662 (1335)	6513 (1439)	81	15	4	0

I = biopsy before training; II = biopsy after training; Co. = control biopsy; VL = m. vastus lateralis; TA = m. tibialis anterior; 0 = normal muscle; + = mild changes; ++ = moderate changes; +++ = moderate to severe changes; ++++ = severe changes; * = end stage muscle; ND = not determined.

and adhesion molecules, were analysed using an immunohistochemical technique (19–21). The cross-sections were stained for macrophages and T-lymphocytes using anti-macrophage (CD68) antibody, anti CD3+ T-cell antibody, anti CD4+ T-cell antibody and anti CD8+ T-cell antibody (19). A human endothelium antibody (EN4) was used as an endothelial marker (20). Adhesion molecules were analysed using an immunoperoxidase method for detection of ICAM-1 or CD54 and VCAM-1 or CD106 (20). Cytokine staining of the cross-sections was performed using anti-IL-1α, anti-IL-1β (21).

Assessment of immunohistochemistry. The number of IL-1β and IL-1ra positive cells and of ICAM and VCAM positively stained capillaries and cells were counted by light microscopy. Positively stained cells and capillaries per total section area were counted and a ratio was calculated based on how many cells and capillaries were positively stained per 4 mm^2 area of the cross-section and evaluated according to the following scoring system: 0 = 0–10 positively stained inflammatory cells; + = 11–25 cells; ++ = 26–50 cells; +++ = 51–100 cells; ++++ = >100 cells per 4 mm^2.

The muscle biopsies were also assessed in a Quantiment 600 (Q600) image analyser (Leica, Cambridge, UK), directed by a PC computer. A special software program, written in high-level language, QUIPS, was used for this application. Image analysis was used to quantify the positively stained area as a percentage of the total tissue section for macrophages (CD68), CD3+ T-cells, CD4+ T-cells, CD8+ T-cells, IL-1α producing cells and EN4 positive endothelial cells. The cross-sectional area of the capillaries stained with EN4 was measured directly from the microscope via a CCD camera (Hamamatsu C3077, Hamamatsu Photonics KK Japan) connected to an image-analysis processor (VIDAS, Kontron Bildanalyse, GmbH, Munich, Germany).

Statistical analyses

Wilcoxon matched pairs test was used to test for significant changes before and after the training. A p-value <0.05 was considered to be statistically significant.

RESULTS

Clinical data

The home exercise program was well tolerated and could be performed by all the patients with the exception of one who experienced difficulty in performing the training program on his own and was assisted by a physiotherapist. Two patients were given the easy exercise program without weight cuffs and 5 patients exercised with the moderate exercise program. Four of these patients used weight cuffs of 1 kg when exercising the upper limbs and 1 used weight cuffs of 2 kg on both upper and lower limbs. None of the patients was able to increase the weights after 6 weeks' exercise. Six of the 7 patients indicated that the training had subjective positive effect on the muscle function, when they were asked about various activities of daily living. None of the patients experienced a deterioration of muscle function.

There were no significant changes in MRC rating before and after the training (Table I). When comparing the baseline and post training peak isometric torque values at angular velocity 120°/s no statistically significant difference was found. Only 4 of the 7 patients completed the 3 assessments. Changes in FI value after the 12-week training period or under the 12-week observation period were not statistically significant.

The mean CK value did not change during training (Table I).

Histopathology

When the general histopathological changes were assessed the degree of histopathology was the same before and after the training in 3 of the patients (Table II). In 1 patient the degree of changes decreased after the training. In 2 patients an increased degree of histopathological abnormalities with end-stage changes was found after the training. These 2 patients (case 1 and 2, Table I) had the longest duration of the disease and were the oldest in the group.

Muscle fibre size and fibre type could not be determined in 2 of the biopsies after the training because of end-stage changes. In the other 4 biopsies, the mean cross-sectional area of type I fibres increased whereas the mean cross-sectional area of type II fibres decreased in 2, was unchanged in 1 and increased in 1 after

the training (Table II). Increase in the percentage of type IIc fibres was seen and there was a decrease in type IIb fibres in 3 of 4 after the training (Table II). However, these changes were not statistically significant. There were no histopathological changes in the 2 control muscle biopsies. Type I area and fibres diameters did not differ from earlier normal controls according to Jakobsson et al. (22).

Immunohistochemistry

All patients had an inflammatory reaction in the muscle biopsies before the training. After the training there were no significant changes in inflammatory cell infiltrates in muscle biopsies assessed as expression of macrophages and CD3+, CD4+ and CD8+ T-cells by immunohistochemistry and image analyses. In all but one of the patients a decrease of macrophage (CD68) staining was found after the training. These changes were, however, not statistically significant.

A significant decrease ($p < 0.05$) was found in EN-4 positive area in the muscle biopsies after the training. A decrease of 46–66% in the EN-4 positive area was found in 5 of 6 biopsies and in the last biopsy the EN-4 positive area was unchanged compared with the biopsy taken before the training period. A decrease in the number of ICAM-1 positive endothelial cells was seen in 3 of 6 patients, in 2 the number was unchanged and in 1 an increase occurred. IL-1α positive area in the muscle biopsies was decreased in 3 of the patients, in 2 there was an increase and in 1 patient the IL-1α positive area was relatively unchanged after the training. The number of IL-1β positive cells was increased in 2 of the patients, unchanged in 3 and in 1 patient there was a decrease in positive cells. These changes were not statistically significant. However, a decrease in the number of IL-1Ra positive cells in 5 of the 6 patients was shown in the biopsies after the training, which was statistically significant ($p < 0.05$) and in 1 patient there were no changes.

The mean diameter of the capillaries in the biopsies before training was 90 μm^2, but 40 μm^2 in the 2 control biopsies. No significant changes were seen in the mean diameter of the capillaries after the training.

DISCUSSION

The home exercise program was well tolerated in the s-IBM patients as previously described in PM and DM (11). All but one of the patients experienced a subjective positive effect on muscle function. This effect may be due to an improved fitness, which would be expected in this group of patients with a relatively prominent motor disability leading to a sedentary lifestyle. There was no increase in muscle strength and muscle function as FI and MRC scores were not significantly increased. This might be due to the low number of patients included, the relatively short training period or to an insensitivity in the tests which were used to measure muscle function and strength. Furthermore, the intensity of the physical training was relatively low compared with the training intensity in the study conducted by Spector et al. (12) in which a significant gain in muscle strength was shown.

However, there was no decrease in muscle strength. A decline in muscle strength can be measured in a few month periods (23, 24). Rose et al. reported a 4% mean decline in muscle strength from baseline in a 6-month period assessed by myometry determining a maximum voluntary isometric contraction (MVIC) (23). Lindberg et al. reported a 1.4% decline in strength from baseline per month as assessed by hand-held myometer (24). Thus, the data from the present study point to that the exercise program may prevent loss of muscle strength.

An increase in muscle fibre pathology was seen in 2 patients. One must consider a true deterioration. No clinical deterioration was found and CK values were unchanged during the training, which argue against a significant deterioration of the muscles during the training. Instead, the differences in outcome of the muscle fibre changes could be due to the fact that the muscle fibre abnormalities have a patchy distribution in IBM, which has been noticed in muscle specimen from an autopsy study (25). The type I muscle fibre cross-sectional area was increased after the training in all of the 4 biopsies in which it could be determined after the training. This was however not statistically significant, but the trend was evident. The difference in the fibre response could depend on the type of training program. Thus, the exercises used in our training program may lead to hypertrophy of type I fibres. An increase in the percentage of type IIc fibres was seen in all biopsies after training. These changes were not statistically significant but one could speculate that this could be due to a muscle fibre transformation. After the training there was a significant decrease in EN-4 positive area in the muscle biopsies, which indicates a decreased endothelial cell area. This could be explained by the trend for an increase in fibre size after the training leading to a lower capillary density as no significant changes were observed in capillary diameter.

Overuse of weak muscle has been described in post-polio patients. The consequences of long-term overuse for the TA muscle fibres were a homogenous fibre type composition with almost only type I muscle fibre and type I hypertrophy (26). In s-IBM an early atrophy of type II fibre and type I hypertrophy has been noticed (unpublished data, S. Arnardottir). In the biopsies after the training no changes in type I percentages were seen and the increase in the fibre cross-sectional area was not statistically significant. With this light intensity training program and no changes in the fibre type composition we do not believe that there is an overuse of the muscles.

It is of great interest to note that all patients were subjects of immunmodulatory treatment, all but one had IVIg treatment. Although the active treatment, all patients had an inflammatory reaction in the muscle biopsies. No significant changes were seen in positive T-cells area or IL-1 positive area and cells after training. Notably, in all but one of the patients there was a decrease in macrophage staining in the muscle biopsies after training. This may suggest a decrease in inflammatory activity after training. A significant decrease in IL-1Ra positive cells was

seen after the training, which also could mean a decrease in inflammatory activity.

The earlier reported findings by Spector et al. (12) indicate that physical exercise may be beneficial to the IBM patients. From the data of this study one might conclude that a moderate home exercise program could also be safely performed in patients with s-IBM, that the program was not harmful to the muscles in s-IBM patients and that this moderate exercise might prevent loss of muscle strength. There is a need for further studies involving a larger patient population and also to determine whether other types of exercise could be more beneficial in s-IBM, in order to gain muscle strength and function.

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