

Case Presentation

Four Clinical Cases Supporting a Therapeutic Rationale for Fibromyalgia

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Received: April 22, 2019; **Accepted:** July 16, 2019;**Published:** July 23, 2019**Abstract****Background:** Fibromyalgia (FM) awaits effective treatment.**Aim of the study:** To offer an etiological treatment based on the hypothesis that a deficient adaptation to common life events leads to a failure to increase the delivery and/or use of oxygen and glucose in muscle fibers and brain neurons.**Methods:** Aerobic exercise is the most often recommended treatment for FM. The proposed treatment is based on rehabilitating the physiological adaptive function by physical exercise through long-term aerobic training (endurance) for about 12 months followed by anaerobic training used as low-level stress stimulation for about 12 extra months. The patients carried out the program at home with simple monitoring of heart rate. During the whole program duration, individual tailoring adjustments are made through successive interactions between patient and medical staff. Interactive support to elicit a reappraisal of individual life organization, including inward-directed attention exercises, is a further important component in the rehabilitation of the adaptive response.**Results:** The paper presents four clinical cases of successful treatment. They are not isolated cases. This concept-based program/treatment was developed and finalized for about ten years. Among eleven FM patients forming the last group, six reached, after 24 months, full or almost full curing, three said they were considerably improved, only two dropped out within the first four months.**Conclusion:** The complete care shown in these four clinical cases indicates that a treatment modality for at least some of the patients with fibromyalgia is at sight. These caring results have been obtained following an etiological rational hypothesis.**Keywords:** Fibromyalgia treatment; Clinical cases; Dysfunctional response to stress; Physical exercise therapy

Introduction

A possible etiologically-based treatment for Fibromyalgia (FM) is proposed, supported by the following hypothesis: FM and failure of the adaptive response to stress are related; FM results from the sustained failure of the adaptive responses to trivial daily events; this sustained failure has a metabolic outcome. Healthy subjects responding to common daily events increase sympathetic and Hypothalamo-Pituitary-Adrenal (HPA) activities, allowing an increased oxygen and glucose consumption for brain neurons and muscle cells. By contrast, subjects with FM responding to common daily events are struggling to carry out their usual life tasks despite failure of their adaptive response: their brain neurons and muscle cells are therefore steadily and repeatedly activated with insufficient metabolic substrates, resulting in metabolic fatigue, poor sleep and muscle pain. The proposed treatment is based on rehabilitating the physiological adaptive function by physical exercise through long-term aerobic training (endurance) for 9–12 months followed by anaerobic training used as low-level stress stimulation. Interactive support to elicit a reappraisal of individual life organization, including inward-directed attention exercises, is a further important component in the rehabilitation of the adaptive response. Four clinical

cases of successful treatment for fibromyalgia are presented here. Authorization to publish these data was obtained from the regional ethics committee (CE CIC- Inter-region Rhone AlpesAuvergne; IRB N°00005921-2015/10/06).

Method and Description of the Program

The program started in 2009 with patients consulting at the Pain Clinic of the Clermont-Ferrand University Hospital. Study inclusion criteria were patients with FM syndrome for at least 6 months, diagnosed following the criteria of the American College of Rheumatology [1], who had not benefited from mind-body approaches in the past. Study exclusion criteria were patients whose main pain was not related to fibromyalgia such as isolated joint pain, cancer, traumatic, infectious, localized neuropathic or degenerative joint pains, or who were treated with opioids and who had already benefited from mind-body treatment. Since its inception the program has been proposed to 6 groups of patients on the basis of one group each year. Fifty-three patients finished the program or dropped out. Patients are included after a first visit to confirm the diagnosis of FM and their willingness to follow a program based on physical exercise. The rationale of the program is explained to them. No past familiarity

with sports activity is required. A second visit (the program visit), is organized with another experimenter who evaluates present physical ability, factors that could trigger or maintain the disease, how readily patients' current life habits can be changed, and their understanding of the program's rationale. An individualized program is initially proposed for two months. Thereafter, it is adapted every two months for two years. The first part of the program is based on practicing aerobic exercise for about one year. Session duration is gradually lengthened from as little as three minutes, three times per week at the start, to reach 45–90 minutes once a week plus 30–50 minutes twice a week at the end of the first year. The maximal heart rate, measured with a heart rate monitor, is tailored to each individual inside an interval (90–125 beats per minute). The exact values of exercise duration and heart rate are individualized during the first program visit and adapted in a group session of 8–14 patients held every 2 months. Individual adjustments are also made on request by the patient to the experimenters by email. Every 3 weeks of aerobic exercise is followed by a semi-rest week when activity is reduced by half. Aerobic exercise is preferably home cycling, but aerobic-based exercise such as running, elliptical bike, swimming, or roller-skating are other possibilities. Group training for inward-directed attention is conducted during the group session. This is designed to foster a mindful attitude when beginning each session of the endurance training.

The second step in the program begins when the experimenters judge that a sufficient duration of endurance sessions has been reached. An anaerobic component is then added to the aerobic program. The proposed anaerobic training exercises are to mimic daily stress occurring in natural circumstances. Exercises such as cycling, running or walking in a natural environment that is not totally flat yield the best results. This represents a natural stimulation for a heart rate increase in the anaerobic range, between 120 and 160 Hz. This effort is felt by the patient, who can spontaneously control both its intensity and duration (a few seconds during the first sessions). This is preferred to a more closely framed anaerobic exercise based on fixed intervals, which tends to elicit excessive efforts. It is probably for the same reason that spontaneous self-regulating responses induced by social dancing also yield good results at this stage of the program. These anaerobic training sessions are proposed once a week. The other two sessions are kept as they were during the end of the endurance phase. The program ends at the patient's request. The patients are told that the physical activity is to be continued afterwards for life. Similarly, it is suggested that personal training for inward-directed attention be continued for life.

Case 1: A man who had suffered a brutal, intense stress event

This patient motivated the program and was the first to follow it. The man was aged 34 years when he first consulted accompanied by his wife, who expressed a caring attitude. His main complaint was pain in the mouth. A diagnosis of burning mouth syndrome was considered. Besides the usual symptoms of intense, long-standing burning mouth with no local visible cause, he described constant widespread muscle pain in both sides of the body, with painful tender points localized on the fingers, hand, arms and legs and abdominal area. He also reported disturbed and non-reparative sleep, sudden unexplained transient paralysis on two occasions, sudden frequent spontaneous tachycardia

episodes, periods of headache, strong spontaneous transient sweating episodes, digestive disorders, strong transient bouts of extreme fatigue, depressed sexual activity, memory-related cognitive disorder, edemas and itching of fingers and hands. The patient had stopped all work and personal activities despite having previously been physically active. His symptom severity scale score was 8 or 9 for a maximum of 12 [1]. Visits to the many dentists and physicians consulted (general practitioners, specialists in neurology, internal medicine, ENT, and maxillofacial surgery) were fruitless, and various examinations (salivary gland biopsy, lumbar puncture and autoimmune blood analyses, brain MRI, ECG) revealed no lesion or dysfunction other than occipital sequelae of meningitis at age six months that left him with impaired vision. After one year of mostly unsuccessful treatment of burning-mouth syndrome with topical and systemic clonazepam, tricyclic antidepressants and several anticonvulsants, a diagnosis of fibromyalgia associated with a burning mouth syndrome was made in 2008. At that time, it was found that the dysautonomic components of the clinical presentation had previously been under-evaluated. The patient related his condition to a personal event that had occurred 5 years before the onset of the symptoms. He had been involved in amorous rivalry with actual physical violence, and had feared for months for his own and his wife's lives. He had been compelled to move away and live in a small flat. A possible link between this intensely stressful event and his condition was considered. The hypothesis was that he was suffering from an impaired physiological stress response, leading to an anarchic, spontaneous burst of ortho-sympathetic activity together with a weak parasympathetic activity. A physical program of rehabilitation of the failing autonomous system was designed and offered to the patient, who accepted it.

A general comprehensive description of the program is given later. For this first patient and treatment, the endurance phase of the program began with home cycling, 5 minutes three times a day, six days a week. After one year of slowly increasing duration of indoor cycling associated with a decreasing number of sessions, the patient was asked to practice outdoor cycling with low gradients. Two years after the beginning of the program, all fibromyalgia symptoms had totally disappeared. BMS symptoms, though much decreased, lasted three more years before disappearing. The patient has been totally free of his previous symptoms of fibromyalgia for eight years since the beginning of the program. He is back at work and has had a normal life for 6 years, including regular outdoor cycling at least once a week.

Case 2: a woman bound by an intense commitment to professional and family activities

AL., born in 1961, is strongly committed to her family. Fibromyalgia was diagnosed in 2011 against a background of periodic episodes of colitis, painful menstruation and several allergic sensitivities. The first symptoms of FM occurred in 2002 after her husband contracted cancer, adding further worry to an already demanding family and work environment. Her symptom severity scale score was 10. Her widespread pain index was 15 for a maximum of 19. She was compelled to dramatically reduce her social interactions, and felt severely hampered in her domestic tasks. She had to reduce her work hours to half time. The discrepancy she felt between what she considered her duty and what she was physically able to do was deeply distressing to her, and greatly lowered her self-respect. Before entering the program, she had followed several

inefficacious treatments based on neurostimulation, and allopathic and phytotherapeutic neuropsychotropic drugs. A hormonal supplementation installed to address menopausal syndromes partially improved asthenia and sleep disorders.

The endurance phase of the program began with home cycling 3 × 10 minutes per day five times a week and swimming once a week. Nine months later she did endurance training for 90 minutes once a week and for 40 minutes twice a week. Heart rate was monitored and maintained between 100 and 120 Hz by the patient. During this period a knee pain appeared, but the patient elected to pursue the program. She was then asked to carry out two to five successive 10-second accelerations followed by a longer time for recovery once a week. Careful gradation was required when introducing this phase of anaerobic training. Heart rate could reach 150 Hz at the end of this phase of the program. The whole program lasted 2 years. On completion of the program, she declared she was pain-free and felt totally cured. Her appraisal was the same 3 years later. She stopped all medication. Importantly, she emphasized that the program helped her change her way of life, in particular with respect to her family and work environments. She no longer felt she had to be of service to everyone around her. She said the program had offered her an opportunity to pay more attention to herself and suspend her ongoing inner stressed state. She was also sure that she would continue the two main components of the program, i.e. physical and inward-directed attention exercises, in her normal life. At the beginning and the end of the program, questionnaire values were 46.6 and 20.0 for the FM impact questionnaire, 11 and 7 for anxiety on the hospital anxiety and depression scale, 9 and 6 for depression on the hospital anxiety and depression scale, 22 and 2 on the catastrophizing scale, 28 and 26.3 on the self-esteem scale, and 53 and 43.3 on the Mos sleep scale. Finally the patient's overall impression of change reached the maximum value of 6 (see questionnaires in 2,3,4). Cortisol waking response was measured from two salivary samples taken 30 minutes apart. Values were 3.7 and 3.4 ng at the start of the program, 2.6 and 4.8 ng at the end of the anaerobic phase, and 4.6 and 13.9 ng at the end of the program. Authorization to publish these data was obtained from the regional ethics committee (CE-CIC-GREN-14-07).

Case 3: a woman bound by an intense commitment to professional and family activities

PP was born in 1954. Fibromyalgia was diagnosed in 2013 against a background of tendinopathy, lumbago, and gonarthrose. Radiography, scintigraphy and serologic analyses excluded poly-arthritis, Lyme syndrome, HIV and other diseases. She had a partial thyroidectomy in 2011. The first symptoms of fibromyalgia appeared gradually in 2013 following accumulation of excessive professional demands that the patient described as very stressful. She was an auxiliary nurse with a heavy workload. She had to take one year of sick leave, and ceased social interactions, particularly dancing activities, which she used to practice two or three times a week. She could not wash, walk or dress by herself. Her widespread pain index was 8 for a maximum of 19, and her severity score was 8. On entering the program at the beginning of 2014, she followed several inefficacious treatments based on neurostimulation and allopathic neuropsychotropics. Home cycling 5 minutes per day 6 times a week was used as endurance training. Nine months after the beginning of the program she did resistance training, resuming dancing, with

a heart rate ceiling of 140 Hz. She considered herself cured after 18 months from the very beginning. At the beginning and the end of the program 18 months later, questionnaire values were: FIQ 58 and 33, HAD (A) 12 and 8, HAD (D) 5 and 3, catastrophizing 32 and 25, self-esteem 25 and 20, Mos sleep 70.4 and 61.4. Cortisol values (Cortisol awaking response) were 2.5 and 2.5 ng at the start of the program, and 15.2 and 12.55 ng at the end of the program. Finally, her overall impression of change was maximum (6) and she declared she felt totally cured. She feels the same 2 years later. She retired from work in the middle of the program, i.e. less than one year after the beginning.

Case 4: a man involved in an activity that is both rewarding and exhausting

CB was born in 1961. This case exemplifies another approach only recently specified. Diagnosis of fibromyalgia was made in 2007 against a background of general anxiety. His father died from cancer when the patient was 16 years old. The symptoms of fibromyalgia appeared gradually following periods of intense hyperactivity due to the accumulation of his main occupation as a primary school teacher and of a second activity as a social volunteer. A sport accident occurred in 1980. He described himself as a perfectionist with an anxious disposition and an addiction to activity. After many bouts of FM, he had stopped sports activity for the previous year. His widespread pain index was 14 for a maximum of 19, and his severity score was 8. He felt greatly disturbed by his hyper-vigilance and was clearly catastrophizing. On entering the program, he was following several inefficacious treatments based on clonazepam, acupan, acupuncture, osteopathy and sophrology. Endurance training was offered with 10 min running three times a week. Strong emphasis was placed on the need not to exceed the program, which was mainly intended to set an upper limit to his physical activity. A quiet, steady activity and regular training for inward-directed attention were the objectives. Fourteen months after the beginning of the program, he was doing three 30 min sessions per week mixing indoor cycling and swimming. No resistance trial was done because it was considered that he was still undergoing stress stimulation from his two activities. He currently declares decreased pain intensity. The endurance training will be continued on the same basis.

At the beginning and end of the program, questionnaire values were: FIQ 32.7 and 26.3, HAD (A) 11 and 10, HAD (D) 2 and 4, [2-4] catastrophizing 20 and 7, self-esteem 29.2 and 20.0, Mos sleep 53 and 32.0. Cortisol values were 5.7 and 5.5 ng at the start of the program and 6.4 and 7.0 at the end. Finally the GIC was 6.

Program rationale

Several studies indicate that a dysfunction of the physiological response to stress is observed in FM and similar dysfunctional conditions [5-10]. This dysregulation involves both the Autonomic Nervous System (ANS) and the HPA axis [11,12], and seems to precede the onset of the disease [5,13]. Its occurrence in some individuals and not in others may depend on a genetic susceptibility [14-16]. It has been hypothesized that this stress response dysfunction is the primum movens of the condition, the consequence of which is impairment of physiological adaptation to trivial daily acute stress events [5,7,13,14]. It is known that not only major stressing stimulation, but also minor repetitive stimulations such as daily harassment or local pain or various types of disease are also associated with FM [13,17]. In

healthy subjects, daily trivial stimulations trigger adaptive responses via cortisol secretion and sympathetic activation including adrenaline blood delivery with no perception of stress by the subject [18]. By contrast, FM subjects display an unresponsive sympathetic system, and a flattened diurnal rhythm of cortisol concentration [5,11,19]. The hypothesis is that a deficient adaptation to common life events leads to a failure to increase the delivery and/or use of oxygen and glucose in muscle fibers and brain neurons normally favored by ANS, adrenaline and cortisol secretion. Muscle fibers and brain neurons are then called on to operate without the required increase in glucose and oxygen. Corresponding pathophysiological processes at the cellular level have been described in FM. Reactive oxygen species produced by oxidative stress and inducing mitochondrial dysfunction could be related to bioenergy alterations and inflammation processes [20,21]. In turn, this may create several possible secondary-induced pathophysiological features such as C fiber neuropathy [22], dysregulation of pain modulation [23,24] and/or central sensitization [9].

Although the link with the main FM symptoms is not fully understood, it makes sense that any causal treatment for FM should enable a return to normal functioning of the HPA axis and ANS in response to common life events (commonly though inappropriately called stress response). Decreased reactivity of the sympathetic system and reinforcement of the parasympathetic tone is sought through aerobic exercises [25-27], and the rehabilitation of the whole stress response reactivity is obtained with gently graduated anaerobic exercises. Similarly, this protocol aims to rehabilitate the deficiency in cortisol response to common life events (stress stimulations) found in FM [28].

An evolving program

Among the fifty-three patients who finished the program or dropped out of it, only eleven patients, including three of the clinical cases described above, have been totally cured. Because of this insufficient outcome and trying to refine the proposed treatment, modifications of the program were carried out each time a new group was initiated.

Four main modifications culminated in the present form of the program. The first problem we had to address was the too-high drop-out rate within the first two-four months of the program. Among the eighty-two patients who entered the program, 30 patients dropped out of the program in the 4 months after the start. During the first years, the program began with 5–10 minutes three times a day during the first months. This meant additional stress for persons already feeling overwrought. We addressed this concern by introducing inward-directed attention training so that the exercise could be viewed as a suspension of daily over-activity. Later, it was found that similar results could be obtained with a much lighter program, particularly at the beginning, so that the program now starts with 5–10 minutes only once a day and three or four times a week.

A second problem was identified at the end of the first phase when moving on to the anaerobic phase. Initially, either of two types of anaerobic training was proposed to the patients. One comprised acceleration/interval exercises drawn from athletic training. It was chosen by persons wishing to be in a closed environment such as their home. The second type of anaerobic training was going outside

to run or bike over hilly ground, or social dancing. This second type of training proved more efficacious, mostly because the patients could act according to how they felt rather than blindly and often too abruptly following heart rate monitoring.

A third problem was later identified when we found out that a subgroup of patients was practicing an intense spare-time activity that was exhausting though self-rewarding. For such patients exemplified by our forth clinical case (CB), we now consider that a major part of the treatment consists in explaining the situation so that they understand that it is their rewarding pastime that is causing the stress leading to the collapse of their physiological stress response system. Particularly with this type of patient, the program must not require any additional activity whatsoever, but instead offer a frame that helps them reduce their physical hyperactivity.

These program modifications were gradually added to successive groups of patients. The results from patients in ongoing programs indicate that the most recently adopted protocols, with three sessions a week from the beginning, very cautious and progressive anaerobic exercise during the second year, and detection of the “happy” hyperactive category of patient are most successful. The group includes eleven FM patients. At the end, after 24 months, six patients are reached full or almost full curing; three said they are considerably improved; only two dropped out within the first four months.

Discussion

FM awaits effective treatment [29]. It is currently considered that FM cannot be cured by any existing therapy [30]. Several studies have pointed to poor outcome of pharmacological treatments, and better results with physical exercises [31,32]. Since the first randomized control trial [33] many experiments have shown some benefit of physical exercise for FM patients. Many forms of exercise have been proposed, either singly or combined: aerobic or anaerobic exercises, strengthening, or flexibility interventions in a land-based or water-based context [34]. Tai chi, yoga, and qigong have also been advocated [35,36]. Aerobic exercise is the most often recommended treatment [37]. Daenen et al. [38] have emphasized that programs must be individually tailored to allow recovery of the homeostatic balance from the stress induced by the exercise itself.

The main limit of this study is the fact that it is not a randomized control trial. However, it must be kept in mind that this concept-based program/treatment was developed and finalized during about ten years. Finally, only the present form of proposal justifies starting a randomized clinical trial. The present program differs from the currently recommended treatments in the following ways:

- (i) It can lead to complete cure in a significant proportion of cases.
- (ii) The treatment derives from an etiologic rationale in which the sideration of the daily trivial adaptive response of HPA and ANS is at the forefront: the metabolic consequence of this physiological failure on brain and muscle cells is thought to play a key role in the mechanisms of the disease.
- (iii) The program is not supervised in a medical context such as in a department of physical medicine, but carried out by the patients themselves at home with simple monitoring of heart rate. This avoids high heart rates, which may prolong the patients' ill state [37,38].

During the whole program duration, individual tailoring adjustments are made through successive interactions between patient and medical staff.

(iv) Anaerobic exercises are proposed only once endurance is fully acquired. The program usually lasts about 24 months. In two reviews including 19 and 16 studies evaluating the benefit of aerobic exercises, the programs are of much shorter duration, ranging from 6 weeks to 6 months [37,39].

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Author Contributions

AW and CB conceptualized the program. AW and PP were responsible for data collection. AW was responsible for drafting the manuscript. All authors contributed to the program design, discussed the results, and commented on the manuscript. Raw data are available at request at the corresponding author's address.

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