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1. Introduction

The EUROMAC consortium was funded by the European Union in 2013 to develop a network and registry for McArdle disease and related disorders. EUROMAC partners are from 13 European centres and also include the USA and Turkey. The aims of the registry are to improve diagnosis and care for people living with these rare disorders and to provide a platform for future clinical trials [1]. On 11–12 July 2014, an exercise testing workshop took place in Madrid, Spain, and was attended by 28 health professionals working in the field of McArdle disease from 8 countries and 13 people living with McArdle disease from 6 countries. This interactive and practical workshop aimed to improve the evaluation of people with McArdle disease and encourage recreational exercise as treatment for people with McArdle disease.

McArdle disease, glycogen storage disease type V (GSDV) is characterized by the absence of muscle glycogen phosphorylase resulting in impaired glycogen metabolism in skeletal muscle. The consequence of this is that muscle pain and fatigue occur within a few minutes of initiating physical activity and is especially severe with strenuous activities and isometric muscle contraction. If the physical activity is not attenuated when symptoms occur, the exercising muscle will go into a rigid contracture leading to muscle pain and fatigue, which is clinically expressed by the improvement in symptoms and a decrease in heart rate (HR) after 8–10 minutes of aerobic activity [2,3]. Once in a second wind, people with the condition may continue to exercise at the same intensity with reduced symptoms. Not only is the second wind phenomenon a diagnostic clue, but it is important in enabling affected people to continue routine activities of daily living.

Advising patients to take regular aerobic exercise training is currently the management approach to improve McArdle patients’ functional capacity as it facilitates skeletal muscle ‘conditioning’ for fatty acid oxidation [4–6]. It also induces muscle vasodilatation, providing greater access to bloodborne free-fatty acids and glucose to exercising muscle, which can oxidize these substrates, attenuating exercise intolerance [7]. Exercise tests are used, as assessment tools, in clinical practice and as outcome measurements in clinical trials because physical examination of these patients may be normal [8]. To date, two exercise tests are used to demonstrate the second wind phenomenon and monitor clinical outcomes in people with McArdle disease named the cycle ergometry test and the 12 minute walk test (12MWT). Cycle ergometry with constant workload can be used to identify the second wind and an incremental exercise test can be used to determine the peak oxygen uptake (VO2peak). The 12MWT can be used to identify the second wind and assess walking speed and distance travelled [3,5,7,9–11]. During the workshop following a series of oral presentations practical sessions on how to perform these exercise assessments were demonstrated.

Strength training in McArdle disease is not usually recommended because of the high associated risk of acute rhabdomyolysis, but at the workshop Dr Alejandro Lucia demonstrated how it is possible for people with McArdle disease to perform this type of exercise without injury [12,13]. The sport scientists advised participants with McArdle disease on how to develop an individualized training programme.
2. The EUROMAC registry

Dr Ramon Marti opened the workshop with a description of the EUROMAC registry, which will collect natural history data from people with McArdle disease and related disorders living in Europe [1,14,15]. The registry has been developed by a network of 17 partners (13 European centres + 5 collaborating partners) from 7 European Union countries, the USA and Turkey. The project, which has been funded by the European Union, aims to raise awareness and increase knowledge with respect to the natural history of these disorders in order to reduce serious complications such as acute rhabdomyolysis and compartment syndrome and to provide a valuable research resource for future studies (Fig. 1). Following full informed consent eligible patients will register and data will be uploaded by specialist physicians via a secure portal on the EUROMAC website. It aims to recruit as many patients as possible from all involved countries [1,16].

3. McArdle disease and related disorders

Dr Ros Quinlivan gave an overview of the pathophysiology of McArdle disease (GSDV) and related GSDs associated with exercise intolerance including GSDVII, GSDXIII, GSD IX and GSDXI. Three main metabolic pathways that provide energy to exercising skeletal muscle were elucidated, namely phosphagens, glycolytic and fatty acid oxidation. Their relation to physical activity intensity and duration were described. The glycogenolytic pathway, which is affected in McArdle disease, provides the main energy source required during the first few minutes of physical activity and for activities requiring isometric muscle contraction. The second wind phenomenon characterized by the improvement in symptoms and heart rate after 8–10 minutes of physical activity is an important diagnostic clue in the history [2,3]. Typical clinical features of McArdle disease were reviewed including a history of exercise intolerance, history of myoglobinuria, muscle hypertrophy, muscle wasting and weakness predominantly affecting upper limb and axial muscles. Muscle contracture with strenuous or isometric activities often leads to acute rhabdomyolysis. It is important to be aware that some patients may report muscle contractures and rhabdomyolysis following routine daily activities that are not necessarily exercise related such as emotionally charged situations (anger, excitement and pain) and during sexual intercourse; thus, symptoms can be induced by everyday activities [17]. Complications of a muscle contracture include acute rhabdomyolysis, renal failure and compartment syndrome. People with McArdle disease often adopt a sedentary lifestyle, which in turn can lead to more muscle weakness and physical deconditioning, obesity and its complications. Patients also report distressing childhood experiences, depression and anxiety. Serum creatine kinase (CK) is frequently higher than 1000 IU/L. The diagnosis may be confirmed by muscle biopsy or genetic studies showing homozygous or compound heterozygous mutations in the PYGM. Muscle biopsy shows myopathic features with subsarcolemmal vacuoles containing glycogen. Histochemical stains show complete absence of the muscle glycogen phosphorylase enzyme. A relatively high frequency of patients have been referred with a false positive diagnosis based upon previous muscle biopsy where the histochemical stain had appeared negative due to technical problems. Thus, the importance of using an internal (blood vessel) and external (normal muscle tissue) control when analysing phosphorylase histochemistry was emphasized.

Management includes appropriate advice on diet and exercise together with psychological support to maintain motivation for keeping active and remaining aerobically fit and avoidance of isometric activities. This is best done with support from a multi-disciplinary team and the benefits of peer support cannot be emphasized enough. Evidence for the potential benefit of regular aerobic exercise in McArdle disease was reviewed and experiences from the annual Association for Glycogen Storage Disease (AGSD)-UK walking course led by Mr Andrew Wakelin were described [18–21]. Increased physical activity levels have been previously correlated with symptomatic improvement in McArdle disease [6,22] as well as with higher health-related quality of life [23]. Regular and moderate physical activity (60–70% of maximal HR, 30–40 minutes a day) 4 days a week for 14 weeks in a group of McArdle patients resulted in an increase in both work capacity and VO2peak [7]. Further studies on aerobic training supported such findings, showing the importance of exercise as a treatment option in McArdle disease [7,8,10]. A case report of resistance training (weight lifting) in an adolescent with McArdle disease was described by Alejandro Lucia (section Strength training exercise in McArdle disease) [13], which was later confirmed by a study on the feasibility and the functional effect of a strength training
3.1. The avoidance–endurance (A-E) model of chronic pain

According to this model, a tendency to rely on avoidance or endurance strategies in response to acute pain can over time lead to a chronic pain syndrome. Individuals falling in the avoidance group experience pain as anxiogenic. There is a hyper-vigilance to pain sensations and activities associated with pain are avoided. Over time, this results in a disuse syndrome with a gradual increase in avoided activities and an increase in associated co-morbidities such as low mood and obesity. For the McArdle patient pain may be associated with contractures and actual or anticipated consequences such as hospitalization and kidney failure. Behavioural and psychological interventions that address this anxiety and break the cycle of avoidance by engaging in the avoided activities can be helpful in this group. Endurance responders in contrast persist with activities by using distraction or minimizing strategies to reduce the pain experience. While this initially leads to positive mood, as goals are achieved, individuals may experience re-current injuries and increasing pain. Over time the strategies may become less effective resulting in negative self-appraisals (‘I am weak’) and low mood. For the McArdle patient endurance strategies risk frequent contractures and more permanent muscle damage with increasing disability over time. These individuals may benefit from addressing underlying beliefs about pain and physical activity in this group may help tailor interventions.

The A-E model permits individuals to switch from endurance to avoidance strategies. This can be easily understood within the McArdle group, for example an individual relying on endurance strategies. This can be easily understood within the framework to help understand the psychological and behavioural processes that underlie the difficulties that some McArdle patients experience with physical exercise. Chronic pain is associated with higher rates of depression, anxiety, sleep disturbance and weight gain, co-morbidities often also seen within the McArdle population. Rommel et al. in a survey of 24 McArdle patients reported a subgroup for whom permanent pain is a major clinical symptom unrelated to age or disease duration [24]. They proposed that gender related genetic factors and maladaptive pain coping may contribute to the development of a chronic pain symptom.

3.2. Data from UK

In order to investigate the prevalence of pain within our group Dr Jatin Pattni presented data from 24 patients attending a specialist McArdle clinic in the UK who completed a measure of quality of life (SF-36v2 [26]) and the Hospital Anxiety and Depression Scale [27]. The SF-36 contains 2 pain related items:

- a. How much pain do you experience (none to very severe)?
- b. How much does this pain interfere in your life (none to extreme)?

The patients reported pain some pain over a 2 week period with only a minority reporting no interference from pain in their daily life. Indeed, half reported moderate to extreme level of interference. Anxiety was also a prevalent feature in our group with half reporting mild to severe levels. There were hints of a trend between the pain items on the SF-36 and results on 12MWT.

These very preliminary comparisons in our group provide some support for the view that pain is a significant factor in the McArdle experience. Exploring the relationship between beliefs about pain and physical activity in this group may help tailor interventions.

4. Exercise tests

Professor John Vissing reviewed outcome measures currently used to assess people with McArdle disease in a research setting together with research outcome measures used to assess other neuromuscular diseases including the 6 minute walk test, quantitative muscle testing, imaging including DEXA and magnetic resonance imaging, muscle biopsy analysis, biomarkers for metabolic changes (such as reduced serum CK levels and a reduction in the frequency of myoglobinuria) and subjective measures usually in the form of questionnaires (including quality of life scores, fatigue measures and indices of disability).

Functional exercise tests include the forearm exercise test consisting of repetitive maximal handgrip contractions every other second for 1 minute (30 contractions) performed under aerobic conditions. During this test and post exercise, blood samples are systematically taken to measure ammonia and lactate levels. In normal individuals there is a 3-fold rise in lactate and ammonia levels whereas in McArdle disease the lactate level does not rise. The use of ischaemia during this test has been challenged as it can trigger muscle damage with a potential for compartment syndrome in patients with McArdle disease. Thus using the test without ischaemia is recommended [28]. Possible complications include pain, swelling, muscle contracture and myoglobinuria; thus the test should be stopped if these symptoms arise. Cycle ergometry can be very useful as a functional outcome measure and to illustrate the second wind phenomenon. During the test, plasma lactate, glucose and ammonia levels are measured. The heart rate is continually monitored and the VO2peak is measured as well. The cycle ergometry test is described in the following sections (Practical session).
5. Practical session

5.1. Exercise testing for the identification of the second wind phenomenon

5.1.1. The cycle test (Dr Alejandro Lucia)

In this session, two adult European patients performed a constant-load (~40 watts or ≥65% age-predicted maximum HR) test using an electrical-magnetically braked cycle-ergometer, in the exercise physiology laboratory of the Universidad Europea (Madrid, Spain) after fasting for at least 2–3 hours. As expected, all showed a decrease in early exertional tachycardia (HR decreasing from ≥150 to ~120 beats per minute) after 7–8 minutes of exercise, which was accompanied by a marked attenuation of local leg muscle pain [29]. Indeed, the first few minutes of this type of exercise act as a warm-up (inducing muscle vasodilation), after which more bloodborne free-fatty acids, as well as some (limited) glucose, are available to the working muscle fibres, which can oxidize these substrates, leading to attenuation of exercise intolerance. Dr Lucia emphasized the importance of fasting 2–3 hours before the exercise testing for the identification of the second wind phenomenon. Haller & Vissing have shown that this may be abolished by glucose infusion [30] or sucrose ingestion before exercise [31].

5.1.2. The 12-minute walk test (12MWT) (Dr Richard Godfrey, Mrs Sherryl Chatfield)

The second wind phenomenon was also demonstrated in one European patient during implementation of the self-paced 12MWT [9,11]. The 12MWT is a relatively simple exercise test, which may be an option to assess patients who have contra-indications for the cycle ergometry test (e.g. joint or additional neuromuscular pathology which limits mobility) [9]. Using this test is cheaper and more practical as it is easier than many other exercise tests to implement and requires no expensive equipment. The test is best performed on a treadmill or on a 20 m length of corridor marked every metre [9], although if space is a problem a 10 m marked length of corridor can be used. Mrs Sherryl Chatfield walked with the participant carrying a visible Borg scale to collect CR10 perceived pain data and HR, while Dr Richard Godfrey monitored the time and recorded the data (distance walked, HR and CR10 scores; Fig. 2). The protocol requires the participant to walk as far as possible in 12 minutes after resting for 30 minutes. HR was measured by wrist watch telemetry (Polar Electro Oy, Finland) and the perceived pain was measured by the Borg CR10 pain scale (Fig. 2) [32]. The patient was advised to slow down/stop when experiencing moderate-strong symptoms (CR10 score higher than 4) [32]. Signs that act as an indicator of achieving second wind are reduction in HR and perceived pain, which normally occurs in this population after approximately 6–8 minutes of walking.

The 12MWT is applied during each clinic visit and the total distance walked is compared from one clinic visit to the next. This reduction in ratios of HR:walking speed and perceived pain:walking speed ratios in association with an increase in total walked distance provides evidence of functional improvement [9].

5.2. VO2peak

Drs Alejandro Lucia and Alfredo Santalla explained the importance of the VO2peak for assessing patients with McArdle disease. VO2peak (also termed ‘VO2max’ when dealing with athletic populations, which requires attainment of an actual plateau in VO2 levels despite further increases in workload) is the peak volume of oxygen that a person can consume upon volitional exhaustion during a dynamic exercise of gradually increasing loads and involving a large muscle mass, e.g., brisk uphill walking, running, bicycling. The VO2peak is the best way to objectively quantify one person’s ‘peak cardiorespiratory fitness’ (or ‘peak aerobic power’) and it is expressed in mL O2/kg/min or in METs (with 1 MET equalling 3.5 mL O2/kg/min). It is a clinically relevant, integrative variable that reflects the peak capacity of the working muscle and therefore reflects the function of different organs and systems (VO2peak = peak cardiac output, i.e., the heart’s peak ability to pump out blood each minute, and muscle’s ability to use oxygen in the blood as it passes through the muscle’s blood capillaries). Furthermore, VO2peak is a strong, independent predictor of health status, because achieving moderate-to-high peak cardiorespiratory fitness (>8 METs) reduces the risk of cardiovascular events and all-cause mortality in middle-aged adults of both genders [33]. Data from the Spanish patients’ registry show very low mean VO2peak levels (~5 METs), yet 7 patients (6 physically active) had a VO2peak ≥ 8 METs, which is not only above the minimum threshold for optimal health but also higher than the previously reported levels (~7 METs) in 2 patients with a ‘mild’ form of McArdle disease owing to residual myophosphorylase activity [34]. The VO2peak of 5 adult European patients participating in this workshop were determined during an incremental cycle-ergometer test to exhaustion (workload increases of 10 watts/min starting at 0 watt). The patients warmed-up for ~20 minutes to elicit the second wind phenomenon and then ingested a carbohydrate drink (equivalent to ~30 grams of sucrose). VO2peak values obtained were <8 METs, but 2 patients (who are physically active) nearly reached the 8 METs-threshold.

6. Strength training exercise in McArdle disease

6.1. The importance of strength training for healthy living

A question that remains overlooked in clinical settings is the feasibility of prescribing resistance (strength) exercises (i.e., weight lifting, exercises with resistance bands, exercise performed against a specific external force that is regularly increased during training) in patients showing exercise intolerance or in debilitated/frail populations. This is an important issue because this type of exercise, together with aerobic exercise, should form part of the routine exercise prescription to maintain and improve health and functional status in most, if not all population groups [35]. We believe it is especially important to promote interventions aiming at increasing the muscle mass and strength of McArdle patients because ‘fixed’ muscle weakness, frequently accompanied by muscle wasting and affecting mostly proximal/trunk muscles in...
a symmetric manner, is prevalent among McArdle patients, e.g., 25% in the Spanish registry, and this problem is further aggravated with ageing [6].

6.2. General recommendations

Drs Alejandro Lucia and Alfredo Santalla described their recently published study illustrating the feasibility of weight lifting exercise in middle-aged McArdle patients [12]. Both instructed all the attending patients on safe performance of strength exercises. They recommend to patients to perform 2 weekly training sessions structured in sets of low-number of repetitions (5–6) with a load (kg) that is associated with a rating of perceived exertion (RPE) of 6–7 on a 0 (=minimum effort) to 10 (=maximum effort) scale, and using a circuit of exercises that involve large muscle groups (bench press, leg press, pull

Fig. 2. The 12MWT workshop log sheet [32].
down/row and abdominals). The low number of repetitions allows the use of muscle phosphocreatine (PC) as the main energy substrate to fuel contraction, with no major reliance on muscle glycogen deposits [36] and thus without causing muscle contractures. In this regard, contractures in McArdle patients might be due to deficient provision of glycogen-dependent ATP supply to Na\(^+\)–K\(^+\) pumps, which can result in down-regulation of these pumps, leading to loss of membrane excitability and exercise-induced hyperkalaemia [37]. The patients’ high sensitivity of their muscle status allows the use of RPE to adequately monitor the loads of strength exercises. The use of large muscle group exercises (bench and leg press) allows exercising with medium-high loads, and the circuit structure, with 2–3-minute rest periods between exercises, is designed to allow for PC to be resynthesized in a given muscle before this muscle is utilized again. Gentle brief stretching exercises are encouraged at the end of each set of repetitions to attenuate muscle stiffness.

7. Workshop assessment

Dr Alejandro Lucía and his team performed familiarization with common strength training exercises (particularly, bench press and half leg squat) as well as muscle strength assessment, in 4 adult McArdle patients inside the gymnasia of the Universidad Europea. Before muscle strength assessment, in order to trigger the occurrence of the second wind in both upper and lower body muscles, patients performed 2 consecutive warm-up sessions of 12-minute duration each, first on an arm-crank and thereafter on a cycle-ergometer. The end of the warm-up was followed by ingestion of a carbohydrate drink (equivalent to ~30 grams of sucrose). After familiarization with the equipment, they performed ‘explosive’ leg half-squats in a ‘Multipower machine’, that was connected to a linear encoder (T-Force Dynamic Measurement System, Ergotech, Murcia, Spain), which has previously proven valid to measure muscle strength (in newtons) and power (in watts) [38]. Patients performed a few sets of 3 repetitions at maximum speed with a 2-minute recovery period between sets (which is long enough to allow for muscle PC stores to be resynthesized). The load or ‘resistance’ (kg) was increased by 2.5 kg in each set. Average strength and power output in the concentric-propulsive phase of the exercise was evaluated in each set [38]. In this type of gradual protocol, both the developed muscle force and power increase with resistance, while the speed of muscle contraction decreases. The test is stopped when the decrease in speed is so pronounced that it coincides with the start of decrease in muscle force. Thus, we recorded the highest value of average power in the concentric-propulsive phase, which typically coincides with the start of decrease in muscle force. The RPE (0–10) after each set never exceeded the value of 7. After assessment, stretching and hydration was performed.

None of the patients reported muscle soreness, pain or contracture during or after the strength training exercises. Although, as expected (given the fact that most patients were untrained) the average power (watts) generated by patients during the concentric-propulsive phase of the half-squat tests (~281 watts) was lower than those we usually find in their age and gender-matched healthy referents (~450 watts), one trained patient (female) reached 405 watts.

8. Conclusion

This report summarized the McArdle Exercise Testing Workshop activities. Exercise testing was broadly covered by both theoretical and practical sessions. Patients’ representative participation, multidisciplinary team involvement, international collaboration and practical training sessions contributed to the success of the event and to the friendly atmosphere. Positive feedback from participants assured the importance of such activities for improving patient care.

9. Future plans

This workshop covered the cycle test, the forearm exercise test and the 12MWT as assessment tools for patients with McArdle disease. They will also be used as assessment tools for evaluating patients for the EUROMAC project.

10. Workshop participants

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