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## Centre of Expertise: Comprehensive Care for Patients with McArdle Disease

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### Abstract

McArdle disease is a rare disease (RD) of muscle metabolism, which is caused by a deficiency of the enzyme myophosphorylase. The cardinal feature of this metabolic myopathy is exercise, or more specifically, activity intolerance. The limited prevalence of this disease translates into a global challenge of limited specialist care for this patient cohort. Without access to informed clinical management, many affected individuals continue to be undiagnosed, misdiagnosed and/or experience delays in diagnosis. And for those that do receive a corrected diagnosis, insufficient access to specialized services often results in inappropriate treatments and adverse consequences for these patients. A Centre of Expertise (CoE) represents the most expansive platform to provide patients with McArdle disease current best practices that encompass thorough assessments, accurate diagnostic methods, relevant information and guidance, multidisciplinary support and an ongoing interface between primary and specialist care. By providing patients with a timely diagnosis and the necessary tools to avoid emergent care and frequent hospitalizations, an overall improvement in health and subsequent reduction in healthcare costs may be seen. To effectuate change, national and regional policies are needed to alter the present course toward a path that is illuminated with enhanced access; with the ultimate goal of improving quality of life (QoL) for all individuals with McArdle disease.

**Keywords:** McArdle disease; Centre of Expertise; Glycogen storage disease; Second wind; Activity intolerance

### Centre of Expertise: Comprehensive Care for Patients with McArdle Disease

McArdle disease is a rare disease (RD) of muscle metabolism, which is caused by a deficiency of the enzyme myophosphorylase. The exact prevalence of this RD is not known; however, it is estimated to be 1: 100,000 in the United States (US) [1], with diagnosed cases being 1: 167,000 in Spain [2] and 1: 232,000 in the United Kingdom (UK) [3]. This metabolic myopathy is equally represented in both sexes and is inherited in an autosomal recessive manner. Affected individuals have mutations in both alleles of the PYGM gene, which encodes myophosphorylase, the skeletal muscle isoform of glycogen phosphorylase [4]. The cardinal feature of this metabolic myopathy is exercise, or more aptly activity intolerance; with symptoms of myalgia, untimely fatigue, stiffness and weakness of involved muscles, dyspnea and tachycardia upon exertion [5].

An interesting and universal objective phenomenon associated with McArdle disease is 'second wind'; which is characterized by a period of less painful and more effective exercise associated with a decrease in heart rate after the initial period of cramping and/or weakness. 'Second wind' generally begins approximately 7-10 minutes after the onset of moderate activity, despite no change in work rate. Although universal, some patients do not recognize the occurrence of 'second wind', however the induction thereof can be identified through objective monitoring [6].

"Many patients with McArdle disease are not diagnosed until adulthood, although most have experienced symptoms from childhood" [7]. In a descriptive study, Reason found the average age of diagnosis (n=283) to be 30.6 years (SD=14.3), yet the average age symptoms were first experienced was 7.4 years (SD=7.6) [8]. Due to the subtle presentation of symptoms, 90% of individuals are misdiagnosed prior to receiving a corrected diagnosis [9].

The hallmark symptom of exercise/activity intolerance is often attributed to being 'out of shape'; as such affected

individuals spend years struggling to improve their overall fitness: most recall having muscle fatigue and cramping since early childhood. Approximately a quarter of patients with McArdle disease develop fixed muscle weakness and wasting of proximal muscles with aging due to repeated muscle damage and years of under activity [10].

Although McArdle disease is not generally considered to be a life-threatening condition, serious consequences may arise. Continued activity in the presence of pain can lead to rhabdomyolysis and the ensuing release of myoglobin to the circulation and kidneys. If too much myoglobin is released, the kidneys can become occluded leading to renal insufficiency and ultimately acute renal failure (ARF). A patient review (N=45) found that approximately 62% of patients had experienced myoglobinuria following intense activity and about 11% had developed ARF, which is almost always reversible [11]. Another potential serious complication is compartment syndrome. If there is sustained isometric muscle contraction, muscle ischemia may lead to inflammation within the fascia. As pressure rises within the compartment, blood flow decreases, leading to compartment syndrome; often necessitating an expeditious fasciotomy [12].

To address the ubiquitous experience of activity intolerance amongst this patient group, it is well documented that regular physical activity (PA) is the best therapy and the main modifier for the clinical course of McArdle disease [10]. However, due to a paucity of available information and services for both patients and clinicians, many patients continue to live a sedentary lifestyle and demonstrate low aerobic power compared to their age-and-sex-matched healthy peers [13].

Herein lies the challenge – without access to efficacious clinical support, affected individuals do not learn the appropriate day-to-day management skills and continue to regard PA as a trigger for symptom occurrence, rather than a safe and effective treatment option. This in turn further impairs the clinical course of their disease [10] impacting both activities of daily living (ADLs) and quality of life (QoL).

To address such challenges, the European Union Committee of Experts on Rare Diseases (EUCERD) recommends the use of a Centre of Expertise (CoE) to provide comprehensive diagnostic and disease management services. This coordinated approach, aids in achieving timely diagnosis, enhanced access to care, reduced healthcare spending and improved patient outcomes/QoL. CoE's either specialize in a single RD or a related group of RDs and provide an array of multidisciplinary services in order to meet the unique medical, rehabilitative, palliative and social needs of RD patients [14]. A CoE offers the following specialized services: consultations, medical examinations, use of specialized equipment, genetic testing, counseling and social care. Additionally, CoEs participate in building healthcare pathways, starting from primary care and contribute to research efforts (e.g. Euromac Registry) through participation in data collection for clinical research and clinical trials.

In the UK, Dr. Ros Quinlivan leads a multidisciplinary team that provides care to over 200 patients with McArdle disease.

The National McArdle Disease and Related Disorders Service (with a London-based clinic) is nationally funded by the NHS England and represents a consummate model for the delivery of McArdle disease health services. To our knowledge no other country operates a clinic as comprehensive as this one that regularly follows a substantial number of patients.

Access to a CoE, similar to the UK clinic, can likely improve the phenotypic manifestation of McArdle disease through active surveillance and proper guidance: access to accurate diagnostic methods, regular assessments (blood work, ECG, aerobic fitness, confirmation of second wind), relevant information and guidance, multidisciplinary support and an ongoing interface between primary and specialist care. Individuals with McArdle disease further benefit from a CoE, as the clinicians/researchers involved are able to gain valuable knowledge and a deeper understanding of the natural history of the disease that other specialists with only a handful of patients are simply not able to do.

As an example, the primary feature of McArdle disease is often referred to in the literature as 'exercise intolerance'. However, it is important to highlight that the insidious impact of this muscle myopathy is not isolated to 'exercise', but rather to all PA. Patients experience an acute energy crisis during most ADLs. And while 'second wind' does provide additional substrates for working muscles, thereby attenuating activity intolerance, the majority of ADLs (hanging laundry, drying hair, changing bed sheets, walking across a parking lot, etc.) do not extend beyond the 7-10 minutes it takes to get into second wind, leaving patients having to constantly struggle in order to maintain a positive energy balance. The nuanced understanding between PA and exercise is well-understood by specialists who actively care for patients with McArdle disease, but unfortunately, most patients do not have an experienced clinician and therefore are simply told to 'not exercise' and even 'stretch muscles which are in contracture', thus causing immense harm.

Through comparative policy analysis, countries that do not have a McArdle disease CoE, are urged to consider development of national/regional health policies that would support transformation of current neuromuscular centres into specialized centres. The creation of national CoEs would help to advance international research efforts; ensure timely and accurate diagnosis, thereby reducing the incidence of serious adverse events; improve access to high-quality patient-centered care; ameliorate disease severity; reduce healthcare spending; and serve as a resource for neighboring clinicians.

While widespread implementation of CoEs may not be realistic, policies that allow for the provision of coordination, cooperation and two-way communication between existing CoEs and other health services may serve as a reasonable alternative. As outlined by the European Organization for Rare Disease (EURORDIS), Reference Networks (RN) provide a consummate model for professionals and CoEs to share knowledge and expertise [15]. Additional support for clinicians/researchers/patients can also be found through the 'International Association for Muscle Glycogen Storage Disease' (IamGSD), whose mission is to enhance the quality of

life of people affected by muscle glycogen storage disease by raising awareness, providing support, advocating the patient viewpoint, disseminating standards and best practice, contributing to research projects, facilitating communications and ultimately reducing the age of diagnosis.

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