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Phenotype and genotype of 197 British patients with McArdle disease: An observational single-centre study

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Abstract

McArdle disease is caused by recessive mutations in *PYGM* gene. The condition is considered to cause a "pure" muscle phenotype with symptoms including exercise intolerance, inability to perform isometric activities, contracture, and acute rhabdomyolysis leading to acute renal failure. This is a retrospective observational study aiming to describe phenotypic and genotypic features of a large cohort of patients with McArdle disease between 2011 and 2019. Data relating to genotype and phenotype, including frequency of rhabdomyolysis, fixed muscle weakness, gout and comorbidities, inclusive of retinal disease (pattern retinal dystrophy) and thyroid disease, were collected. Data from 197 patients are presented. Seven previously unpublished *PYGM* mutations are described. Exercise intolerance (100%) and episodic rhabdomyolysis (75.6%) were the most common symptoms. Fixed muscle weakness was present in 82 (41.6%) subjects. Unexpectedly, ptosis was observed in 28 patients (14.2%). Hyperuricaemia was a common finding present in 88 subjects (44.7%), complicated by gout in 25% of cases. Thyroid dysfunction was described in 30 subjects (15.2%), and in 3 cases, papillary thyroid cancer was observed. Pattern retinal dystrophy was detected in 15 out of the 41 subjects that underwent an ophthalmic assessment (36.6%). In addition to fixed muscle weakness, ptosis was a relatively common finding. Surprisingly, dysfunction of thyroid and retinal abnormalities were relatively frequent comorbidities. Further studies are needed to better clarify this association, although our finding may have important implication for patient management.

KEYWORDS

comorbidities, McArdle disease, muscle glycogen phosphorylase, pattern retinal dystrophy, rhabdomyolysis, thyroid dysfunction

Synopsis

Extramuscular comorbidities such as thyroid dysfunction and pattern retinal dystrophy are quite common in patients with McArdle disease, a finding that may have important implications for patient management.

1 | INTRODUCTION

McArdle disease, also known as glycogen storage disease type V, is a genetic condition caused by recessive mutations in the *PYGM* gene on chromosome 11, encoding the muscle isoform of glycogen phosphorylase (also known as myophosphorylase). The first description dates back to 1951 by the Scottish physician Brian McArdle,[1] who suspected a deficiency in glycogen metabolism in a patient who could not produce lactate during ischaemic exercise; however the underlying defect in muscle phosphorylase was later described by Mommaerts et al.[2] in 1959 and the genetic cause was not discovered until several years later.[3] Despite being considered a rare disorder, with an estimated prevalence between 1:100 000 and 167 000,[4,5] McArdle disease is the most common muscle glycogenosis.[6] Deficiency of myophosphorylase prevents the metabolism of glycogen in skeletal muscle cells leading to an inability to generate energy from glycogenolysis.[7]

In essence, McArdle disease is clinically characterized by childhood or early adult onset of exercise intolerance, muscle fatigue, myalgia, contractures and episodes of rhabdomyolysis induced by brief intense isometric and anaerobic exercise.[7] The "second wind" phenomenon is consistently recognized in these patients and it is defined as an improvement of exercise-induced myalgia and tachycardia after a short period of rest with the ability to resume the exercise easily 8 to 10 minutes after the onset.[6] Laboratory tests show persistently elevated resting serum creatine kinase (CK), myoglobinuria, and possible evidence of renal failure after episodes of rhabdomyolysis.[8] Molecular genetic testing (sequencing of *PYGM* in circulating leukocytes),[9] has replaced direct assay of myophosphorylase activity, obtained via a muscle biopsy,[10] as the most helpful initial diagnostic test.

Three different isoforms of glycogen phosphorylase exist and PYGM is the one predominantly expressed in skeletal muscles.[11] As such, McArdle disease has always been considered a "pure" myopathy. Descriptions of extramuscular manifestations are rare; although in recent years, there have been a very small number of people with McArdle disease reported to have pattern retinal dystrophy (PRD).[12-16] Anecdotally, our group has observed frequent thyroid involvement in these patients and a first report has been recently made.[17] Following these observations, more attention has been paid by our team to detect possible extramuscular manifestations, with a particular interest in thyroid function and retinal abnormalities.

In this observational study, we assess the genotype and the phenotype of McArdle disease in a large cohort of British patients with a genetically confirmed diagnosis. Descriptions of large cohorts (>50 patients) are not common, and they have mainly focused on muscle phenotypic features only.[4,18-21] As such, our study aims to contribute to this growing area of research by exploring muscular and extramuscular manifestation in a cohort of patients with McArdle disease.

2 | MATERIALS AND METHODS

2.1 | Patients

Clinical and laboratory data of 197 patients with a genetically confirmed diagnosis of McArdle disease were collected between 2011 and 2019. All the patients underwent at least one visit to the highly specialized clinic for McArdle Disease and Related Disorders at the MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery (NHNN), London. Since 2010, the service has prospectively collected standardised data stored in a patient electronic health record system and secure database. Collected data included: demographics, genotype data, and phenotype data focusing on muscle function and other co-morbidities.

Approval for this study was granted by the Institution internal review board. Informed consent was not required as the data were collected as part of routine clinical practice.

2.2 | Genotype

In all patients, the mutant *PYGM* alleles were identified in blood using standard protocols. The two most common mutations found in Caucasian patients, p.Arg50* and p.Gly205Ser, were screened in all patients. In case of heterozygous or negative result, a Sanger sequencing of the entire coding region and intron/exon boundaries of *PYGM* was performed.[22] In some cases, a panel of 30 genes associated with acute rhabdomyolysis/metabolic myopathy,[23] including sequencing of *PYGM* gene, was performed (Illumina HiSeq2500).

2.3 | Phenotype

Clinical histories were assessed and data on exercise performance, rhabdomyolysis, episodes of acute renal failure, second wind phenomenon, frequency of painful muscle contractures, pattern and degree of muscle weakness and history of gout were collected. At each visit, patients undertook a 12-minute walk test to assess muscle exercise tolerance. Muscle strength was assessed using the MRC 5-grade score.[24]

Blood tests were routinely performed at each clinic visit and analysed in the accredited biochemistry laboratory at University College Hospital London.

Routine blood tests included full blood count, liver and renal function, basal serum CK, uric acid, serum free T4 and TSH, anti-thyroid peroxidase antibodies (TPO-Ab). Thyroid status was also determined by medical history, including regular treatment with levothyroxine, or previous history of thyroid cancer.

The ophthalmic examination was performed by two of the authors (O. A. M. at Moorfields Eye Hospital, London, and K. N. K. at Leeds Centre for Ophthalmology, Leeds, UK). Assessments included best-corrected visual acuity (Snellen), slit-lamp biomicroscopy and detailed retinal imaging—ultra-widefield colour and autofluorescence fundus photography (Optos, Dunfermline, UK), spectral domain optical coherence tomography and short wavelength fundus autofluorescence imaging (Heidelberg Engineering, Heidelberg, Germany). Following referral to our service of two patients with visual impairment due to PRD, our aim is to routinely screen the entire cohort of McArdle subjects. So far, we have screened 41 patients, who were randomly selected via routine clinic appointment.

2.4 | Statistical analysis

Descriptive data are expressed as mean ± SD. The prevalence of muscle, thyroid, and retinal comorbidities was calculated as frequency (%) in our population. t-Test was used to analyse the difference between the mean age of patients with and without hypothyroidism, with and without PRD and, within patients with PRD, the mean age of asymptomatic vs symptomatic patients. Difference in frequency of sex at birth in patients with or without PRD was compared using the Chi statistics. To compare rates of hypothyroidism and PRD in the two most common *PYGM* mutations, Chi statistics was used. If the cell counts were less than five, Fisher's exact test was used instead.

A $P < .05$ was considered significant. Analyses were performed with software (SPSS v. 19.0 for Windows; SPSS Inc.).

3 | RESULTS

3.1 | General features

Data from 197 patients with a genetic diagnosis of McArdle disease were retrospectively analysed. Patients were equally distributed between male and female (n = 96, 48.7% female). The mean age of patients at observation was 48.4 ± 16.5 years. Despite the majority of individuals (92.9%, n = 183) being symptomatic in

childhood, usually in the first decade, the disease was diagnosed at a mean age of 34 ± 15.8 years. Data are shown in Table 1.

3.2 | Genotype

The genetic analysis has detected at least one copy of the commonest Caucasian stop codon pathogenic variant c.148C > T (p.Arg50* or R50X) in the majority of patients. In fact, 95 patients (48.2%) were homozygous for the R50X pathogenic variant, 30 (15.2%) were compound heterozygous for R50X and the second most common Caucasian mutation c.613G > A (p.Gly205Ser or G205S), and 4 (2%) were homozygous for the G205S mutation. Forty-six patients (23.3%) were compound heterozygous for R50X and a second pathogenic variant different from G205S. See Table 2 for the list of mutations identified in

TABLE 1 General features and main muscle phenotype of our cohort

Total patients, n	197
Gender	
Female	96 (48.7%)
Male	101 (51.3%)
Current mean age, y (SD)	48.4 (±16.5)
Age at diagnosis, y (SD)	34 (±15.8)
Symptom onset	
Paediatric age (<18 years), n (%)	183 (92.9)
Adult age, n (%)	6 (3)
Not known, n (%)	8 (4.1)
Mean baseline Serum CK, (SD)	2892 U/L (±3716)
History of rhabdomyolysis, n (%)	149 (75.6)
History of muscle contracture, n (%)	137 (69.5)
History of second wind, n (%)	178 (90.4)
History of acute renal failure, n (%)	12 (6.1)
Dialysis, n (%)	7 (3.6)
Compartment syndrome, n (%)	3 (1.5)
Hyperuricaemia, n (%) (urate n.v.: 175-363 μmol/L)	88 (44.7)
Gout, n (%)	22 (11.2)
Muscle weakness, n (%)	82 (41.6)
Ptosis, n	28 (26 bilateral)
Paraspinal, n	59
Upper limbs (proximal), n	39
Lower limbs (proximal), n	21
Scapular winging, n (%)	24 (13 bilateral)

Note: n = number; y = years; SD = standard deviation; n.v. = normal values.

TABLE 2 PYGM mutations identified in our 197 McArdle patients

Type of mutation	N°	%
p.Arg50* (c.148C > T)/p.Arg50* (c.148C > T)	95	48.2
p.Arg50* (c.148C > T)/p.Gly205Ser (c.613G > A)	30	15.2
p.Arg50* (c.148C > T)/p.Pro489Arg (c.1466C > G)	7	3.6
p.Gly205Ser (c.613G > A)/p.Gly205Ser (c.613G > A)	4	2.0
p.Arg50* (c.148C > T)/p.Gly449Arg (c.1345G > A)	4	2.0
p.Gln567Pro (c.1700A > C)/p.Gln567Pro (c.1700A > C)	3	1.5
p.Arg50* (c.148C > T)/p.Arg270* (c.808C > T)	3	1.5
p.Lys754Asnfs*49 (c.2262delA)/p. Lys754Asnfs*49 (c.2262delA)	3	1.5
p.Arg50* (c.148C > T)/p.Asn377Tyr (c.1129A > T)	2	1.0
p.Arg50* (c.148C > T)/c.425-26A > G	2	1.0
p.Arg50* (c.148C > T)/p.Arg139Trp (c.415C > T)	2	1.0
p.Arg50* (c.148C > T)/p.Ala822Asp (c.2465C > A)	2	1.0
p.Leu5Argfs*21 (c.14delT)/p.Leu5Argfs*21 (c.14delT)	2	1.0
p.Arg576* (c.1726C > T)/p.Arg576* (c.1726C > T)	2	1.0
p.Arg50* (c.148C > T)/p.Trp798Arg (c.2392 T > C)	2	1.0
p.Arg50* (c.148C > T)/p.Lys609Lys (c.1827G > A)	1	0.5
p.Arg50* (c.148C > T) /c.345 + 2 T > A	1	0.5
p.Arg50* (c.148C > T)/p.Glu797Valfs*18 (c.2385_2386del)	1	0.5
p.Arg50* (c.148C > T)/p.Ala365Glu (c.1094C > A)	1	0.5
p.Arg50* (c.148C > T)/**p.Ala452Argfs*23 (c.1353dupC)**	1	0.5
p.Arg50* (c.148C > T)/p.Gly686Arg (c.2056G > A)	1	0.5
p.Arg50* (c.148C > T)/c.425-2A > G	1	0.5
p.Arg50* (c.148C > T)/p.Gln577Arg (c.1730A > G)	1	0.5
p.Arg50* (c.148C > T)/**p. Asn632_Asp634del (c.1894_1902del)**	1	0.5
p.Arg50* (c.148C > T)/p.Leu292Pro (c.875 T > C)	1	0.5
p.Arg50* (c.148C > T)/p.Val239del (c.715_717del)	1	0.5
p.Arg50* (c.148C > T)/p.Arg94Trp (c.280C > T)	1	0.5

TABLE 2 (Continued)

Type of mutation	N°	%
p.Arg50* (c.148C > T)/p.Lys575Glu (c.1723A > G)	1	0.5
p.Arg50* (c.148C > T)/c.1768 + 1G > A	1	0.5
p.Arg50* (c.148C > T)/**p.Glu699* (c.2095G > T)**	1	0.5
p.Arg50* (c.148C > T)/p.Gly695Arg (c.2083G > A)	1	0.5
p.Arg50* (c.148C > T)/p.Arg650* (c.1948C > T)	1	0.5
p.Arg50* (c.148C > T)/**p.Lys78* (c.232A > T)**	1	0.5
p.Arg94Trp (c.280C > T)/p.Arg650* (c.1948C > T)	1	0.5
p.Arg94Trp (c.280C > T)/p.Gly695Arg (c.2083G > A)	1	0.5
p.Arg94Trp (c.280C > T)/c.1969 + 221_2177 + 369del	1	0.5
p.Leu116Pro (c.347 T > C)/p.Arg602Gln (c.1805G > A)	1	0.5
p.Gly455Arg (c.1363G > C)/p.Lys609Lys (c.1827G > A)	1	0.5
p.Gly205Ser (c.613G > A)/p.Arg576* (c.1726C > T)	1	0.5
p.Gly205Ser (c.613G > A)/c.425-26A > G	1	0.5
p.Trp183* (c.549G > A)/p. Ala452Argfs*23 (c.1353dupC)	1	0.5
p.Leu36Pro (c.107 T > C)/c.1239 + 1G > A	1	0.5
p.Ala452ArgfsTer23 (c.1353dupC)/p. Arg771Gln (c.2312G > A)	1	0.5
p.Gln176* (c.526C > T)/p.Gln176* (c.526C > T)	1	0.5
p.Met1Val (c.1A > G)/p.Met1Val (c.1A > G)	1	0.5
p.Arg161Cys (c.481C > T)/p.Arg270* (c.808C > T)	1	0.5
Homozygous deletions exon 1-5	1	0.5
p.Arg50* (c.148C > T) /second mutation unknown (but no detectable myophosphorylase activity on muscle biopsy)	2	1.0

Note: Previously unpublished mutations are in bold.

our cohort, including seven previously unpublished pathogenic variants.

3.3 | Phenotype

Exercise intolerance affected all patients, with onset of symptoms soon after initiation of activity. Episodic rhabdomyolysis was the second most common muscular

TABLE 3 Thyroid dysfunction in our cohort

	N°	%	Mean age, y (SD)
Thyroid dysfunction (total)	30	15.2	54.1 ± 15.0
Normal thyroid function	167	84.8	47.4 ± 16.6[a]
Hypothyroidism	24	80	56.4 ± 15.3[a]
Female/male	15/9	62.5/37.5	
Overt hypothyroidism	18	75	57.6 ± 14.2
Subclinical hypothyroidism	6	25	47.5 ± 17.9
Hyperthyroidism	4	13.3	46.5 ± 13.2
Female/male	3/1	75/25	
TPO-Ab, normal TSH	2	6.7	54 ± 9.9
Female/male	1/1	50/50	

Note: y = years; SD = standard deviation; TPO-AB = anti-thyroid peroxidase antibodies.
[a]Subjects with hypothyroidism are older than subjects with normal thyroid function: *P* = .003.

TABLE 4 Pattern retinal dystrophy in our cohort

Pattern retinal dystrophy	N°	%	Mean age, y (SD)
Ophthalmic evaluation	41	20.8	
Present	15	36.6	61.9 ± 9.7[a]
Female/male	1/14[b]	6.7/93.3	
Subclinical pattern retinal dystrophy	8	53.3	56.8 ± 10.1[c]
Pattern retinal dystrophy with clinical symptoms (reduced visual acuity)	7	46.7	67.9 ± 4.7[c]
Absent	26	63.4	44.5 ± 13.8[a]
Female/male	15/11[b]	57.7/42.3	

Note: y = years; SD = standard deviation.
[a]Subjects with pattern retinal dystrophy are older than subjects without it: *P* = .00011.
[b]Pattern retinal dystrophy is more common in males: *P* = .0021.
[c]Subjects with symptomatic pattern retinal dystrophy are older than asymptomatic subjects: *P* = .019.

symptom in our cohort: 75.6% (n = 149) of patients experienced at least one episode of rhabdomyolysis. Acute renal failure was a complication of rhabdomyolysis in 6.1% (n = 12) of patients and in seven of them dialysis was required. In three patients (1.5%), rhabdomyolysis was complicated by compartment syndrome requiring decompression. Episodes of muscle contracture were a common symptom, reported by 137 patients (69.5%). Self-reported second wind phenomenon or assessed at the 12-minute walk test was recognised by the vast majority of patients (n = 178, 90.4%).

With regard to laboratory tests, 100% of patients had high baseline CK (2892 U/L ± 3716). Hyperuricaemia (urate >363 μmol/L) was observed in 88 patients (44.7%). Of note, 11.2% of patients (n = 22) had a positive history of gout.

Fixed muscle weakness was observed in 82 patients (41.6%) and it mainly involved paraspinal muscles (n = 59), proximal upper (n = 39), and lower limbs

(n = 21). Mild to moderate ptosis was present in 28 patients and it was usually bilateral and symmetrical (n = 26). Scapular winging was observed in 24 patients (12.2%) and in 13 subjects was bilateral.

See Table 1 for details.

Thyroid dysfunction was present in 30 subjects (15.2%; see Table 3 for details). The majority of them (n = 24) had hypothyroidism, four presented with hyperthyroidism, and two had positive TPO-Ab with normal thyroid function. Papillary thyroid cancer was the cause of secondary hypothyroidism in three subjects. People with hypothyroidism were significantly older than those with normal thyroid function (56.4 ± 15.3 vs 47.4 ± 16.6; *P* = .003). Of note, as two patients with positive TPO-Ab and normal TSH are at risk of developing overt hypothyroidism,[25] they continue to be monitored.

In 15 subjects (36.6% of patients that underwent ophthalmic examination, Table 4), relatively symmetrical changes in the outer retina (accumulation of hyperautofluorescent outer
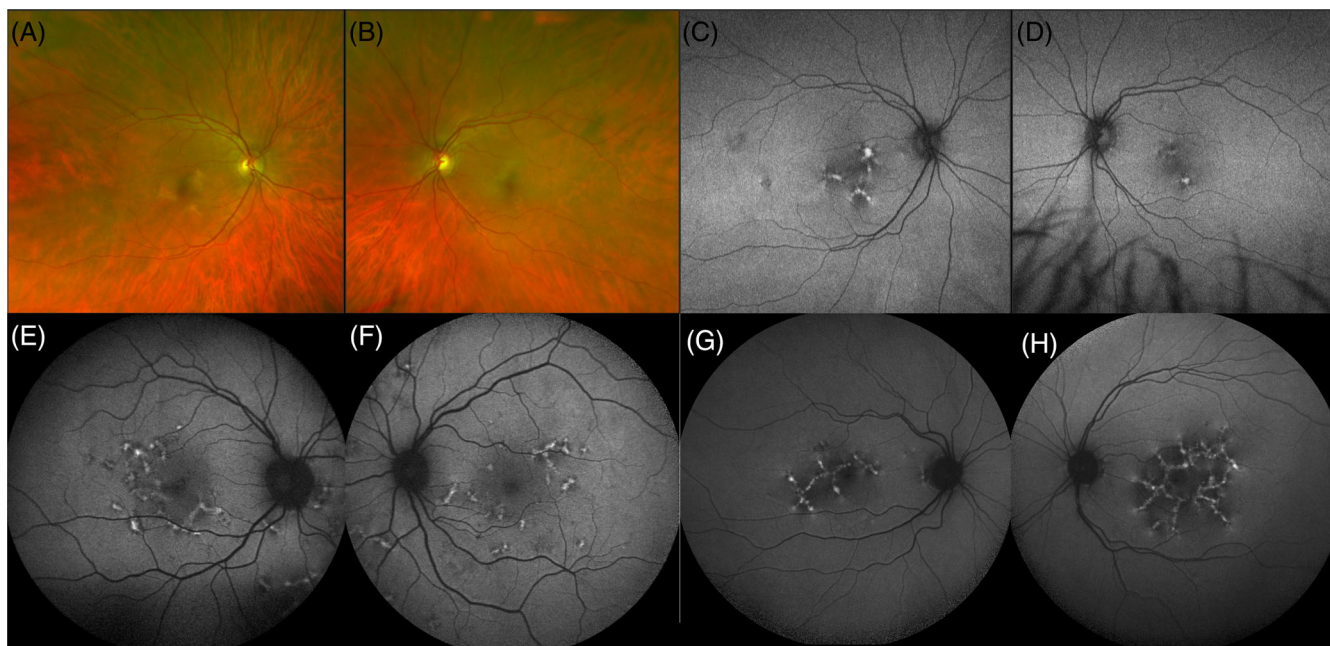
FIGURE 1 Multimodal fundus imaging of pattern retinal dystrophy. (A,B) Pseudocolour retinal images and (C,D) fundus autofluorescence from a 69 years old male patient with McArdle disease. Images show bilateral, symmetrical reticular pigment at the macula. (E-H) Blue light fundus autofluorescence of two males with McArdle disease. Images show bilateral hyperautofluorescent pattern-shaped deposit

retinal deposit with or without associated outer retinal atrophy) consistent with a diagnosis of PRD were detected (Figure 1). Males were more commonly affected than females (14:1). The mean age of patient with PRD was 61.9 ± 9.7 years. In 7/15 patients, PRD was associated with a symptomatic reduction in visual acuity; these patients were significantly older than patients with PRD who recorded normal vision ($P = .019$). In most patients, PRD was bilateral, although in two cases, including the only female with PRD, it was unilateral. Choroidal neovascularisation was not observed or suspected in any patients. Other retinal abnormalities detected in our population include retinal detachment leading to loss of vision, documented in three subjects.

Genotypes did not differ between patients with or without thyroid dysfunction and with or without PRD. Furthermore, we did not find any difference between rates of prevalence of hypothyroidism or PRD in patients homozygous for the truncating mutation R50X and patients heterozygous for the truncating mutation R50X and the missense mutation G205S ($P = .51$ for hypothyroidism and $P = .3$ for PRD).

4 | DISCUSSION

This is one of the largest reported cohorts of patients with McArdle disease and, as such, it adds further insight into the natural history of this rare condition. In this study,

we have characterized the genotype and phenotype of our cohort and some novelties are described.

4.1 | Muscle phenotype

McArdle disease has been considered to be a "pure" skeletal muscle disorder presenting with exercise intolerance, muscle contracture and rhabdomyolysis, second wind phenomenon and fixed muscle weakness, as demonstrated in our cohort. We found fixed muscle weakness in 41.6% of our patients, with a median age of 60 years. The rate of fixed weakness in our cohort is lower than that in a recent description by Scalco et al.[17] who found fixed weakness in 51.4% of patients. This can be influenced by the tailored exercise recommendation for strengthening muscles that patients receive in our specialised clinic, which can help in preventing fixed muscle weakness later in life. Fixed muscle weakness can develop in older patients[7] and localises in paraspinal muscles and proximal muscles, affecting upper limbs more than lower limbs. In our cohort, the distribution of weakness is in line with previous reports.[4,7,17] Rhabdomyolysis episodes can be severe and lead to renal failure.[26] In our cohort, this was observed in 12 patients with seven of them requiring dialysis, demonstrating that this is a relatively rare but severe complication. Then, 100% of our patients had high resting CK, an important element that can raise

the suspicion of McArdle disease in the presence of other typical symptoms. These data are in line with a previous description of a large Spanish cohort of McArdle patients.[18]

Increased plasma urate level is a known complication of several metabolic myopathies and it is probably due to excessive degradation of muscle purine nucleotides, secondary to impaired ATP generation.[27] Patients with hyperuricaemia (44.7% in our cohort) are at risk of gout, a complication observed in 25% of them, hence the importance of monitoring urate level regularly in people with McArdle disease.

The presence of ptosis in McArdle disease is not a well-recognised feature. However, it has been described before by Cheraud et al.[28] who presented two patients with bilateral ptosis, limb girdle myopathy and a new *PYGM* mutation, and in a recent paper by Scalco et al.[17] where ptosis was described in eight of the 269 European adults with McArdle disease. In the present study, we confirm ptosis to be a feature of McArdle disease. In fact, in our cohort, it was described in 28 subjects (14.2%), it was mild/moderate and bilateral in most cases. No signs of external ophthalmoplegia or muscle fatigability were noted. As ptosis has also been previously observed in Pompe disease, another muscle glycogenosis,[29] it should be considered in the differential diagnosis of these disorders.

McArdle disease may not be recognised by non-neuromuscular physicians; this is testified by the 15 to 20 years of diagnostic delay, similar to previous reports.[30] The stop codon R50X is the commonest pathogenic variant in the British population,[31] followed by G205S. Specifically investigating British patients for these two mutations is quick and cost-effective; however, a negative result does not exclude the diagnosis.

4.2 | Extramuscular comorbidities

Surprisingly, our study shows that thyroid disease was a relatively common complication, hypothyroidism being more common than hyperthyroidism. In Britain, the prevalence of hypothyroidism is 2% in the general population and 5% in people over 60 years of age,[32] a lower frequency than observed in our cohort (12.2%). As the prevalence of hypothyroidism increases with age, the age of patients with underactive thyroid in our cohort was elevated compared to those with normal thyroid function ($P = .003$). Women were affected twice as often as men (62.5% vs 37.5%). The finding of thyroid papillary carcinoma affecting three patients in our cohort was unexpected. In fact, papillary thyroid cancer is rare and it has been shown to be more common in people who have Graves' disease.[33]

With regard to PRD, 15 out of 41 (36.6%) patients who underwent an ophthalmic screening were found to manifest signs of this retinal dystrophy. Of note, 4 of the 15 patients with PRD have been previously described by Mahroo et al.[16] The term PRD is a historic one, used to describe a retinal phenotype that is characterized by foci of pigment deposition in the retina.[34] With time, cellular dysfunction, either at the level of the retinal pigment epithelium or the photoreceptor, results in outer retinal atrophy, and consequently loss of vision, if the central macula is affected. Often, retinal examination can identify areas of metabolic distress prior to the development of symptoms. This is important when counselling patients regarding the natural history of their condition, and in highlighting the very low risk of choroidal neovascularisation, a potentially treatable form of sight loss. Screening for ocular involvement by asking patients about (a) their ability to read small print when wearing reading glasses or (b) the presence of distorted vision (metamorphopsia) can potentially identify changes associated with PRD, which would warrant referral to an ophthalmologist. As expected, patients with PRD were significantly older than those without it (61.9 ± 9.7 vs 44.5 ± 13.8, $P = .00011$). Furthermore, 46.7% of patients reported reduced visual acuity and this group was older than the group with subclinical PRD (67.9 ± 4.7 vs 56.8 ± 10.1, $P = .019$). This result is in line with the natural progression over time of PRD. Unexpectedly, we found an increased prevalence of PRD in men (14:1) compared to women ($P = .002$).

Our results describe for the first time in a large population of McArdle patients all attending the same specialised clinic, the presence of retinal and thyroid comorbidity. The finding was surprising and may support the hypothesis that mutation in *PYGM* might cause disruption of extramuscular tissues.

Interestingly, the tissue expression of PYGM is not restricted to skeletal muscle.[35,36] In fact, its expression was recently found in human T lymphocytes, retinal pigment epithelium cells and thyroid follicular epithelial cells.[37,38] The absence of PYGM expression in thyroid and retina modifies their biological functions affecting mitochondrial stress and glycolytic rate.[37] The most common thyroid dysfunction in our cohort was hypothyroidism, that is generally caused by an autoimmune condition called Hashimoto's disease. T lymphocytes have a main role in the pathogenesis of this condition.[39] Given the important role of the interaction between PYGM and the small GTPase Rac1 in T-cell migration and proliferation,[40-42] we can speculate that mutations in *PYGM* could disrupt this mechanism leading to an abnormal immune mediated response. In addition, PYGM is not just involved in glycogenolysis. The absence of the enzyme does not only affect the ability to generate ATP but it also

has an impact in the post-translational modifications (PTM) that happen in intracellular proteins.[43] PTM O-glycosylation process is involved in cellular survival signals, response to acute stress and tumour growth.[44] Therefore, it seems that the role of PYGM is broader than expected, including cell regulatory functions that impact intracellular processes. However, mechanistic studies showing how PTM processes are altered in McArdle patients are needed and may be the focus of future research.

Our study has some limitations. Despite being one of the largest cohort of patients with McArdle disease, this is a retrospective study based on already existing data routinely collected between 2011 and 2019 in our centre. A note of caution is due here since further laboratory work is necessary to definitely establish a link between thyroid and retinal comorbidities and McArdle disease. Moreover, multicentre registry for patients with McArdle disease, such as the EUROMAC registry,[17] will be helpful in future to collect broad clinical data in larger cohort of patients.

5 | CONCLUSION

In conclusion, within the muscular involvement, we confirmed that ptosis is a possible clinical feature of McArdle disease and we describe the prevalence of hyperuricaemia and gout in a large cohort of patients. We broadened the spectrum of mutation in *PYGM* causing McArdle disease. Lastly, we described how thyroid dysfunction and PRD are commonly present in our cohort. Therefore, it is possible to hypothesize that a connection exists between *PYGM* mutation and extramuscular manifestation and this is corroborated by the fact that *PYGM* is expressed in several tissues, including thyroid and retina. However, several questions remain unanswered at present and further research should be undertaken to investigate this link.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
Chiara Pizzamiglio: Was involved in study design, data collection, data analysis, and wrote the first and final version of the manuscript. **Rosaline Quinlivan**: Was involved in study design, data collection, data analysis, and wrote the first and final version of the manuscript

and is guarantor for the article, accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. **Omar A. Mahroo**, **Kamron N. Khan**, and **Maria Patasin**: Contributed to data collection and revised the manuscript for intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. All authors confirm the absence of previous similar or simultaneous publications.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. There are no personal identifying data included in this article.

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