CLINICAL AND GENETIC ASPECTS IN 20 ITALIAN PATIENTS WITH GLYCOGENOSIS TYPE V (MCARDLE DISEASE)

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INTRODUCTION

McArdle's disease, also known as glycogen storage disease type V, is caused by a deficiency of myophosphorylase, an enzyme encoded by the PYGM gene with an estimated prevalence of about 1:100,000–1:167,000. Although is one of the most common metabolic myopathies, there are still few published epidemiological data (Lucia et al. 2012).

Patients with McArdle's disease clinically complain of exercise intolerance, fatigue, cramps, and muscle contractions. They also commonly experience episodes of rhabdomyolysis and myoglobinuria, mainly triggered by physical exercise. The onset of symptoms is usually reported during the second or third decade of life, however, some early onset cases have been reported (Arenas et al. 2009) as well as patients with atypical clinical manifestations (Lucia et al. 2012).

Currently, more than 100 mutations in the PYGM gene, have been described worldwide, but one, p.R50X, has been found to be the most prevalent in many different ethnic groups.

We report, herein, clinical, biochemical and molecular genetic features of 22 McArdle patients studied in our Center

Materials and Methods

22 patients (13 M, 9 F), diagnosed at our Neuromuscular Center over the last 20 years, were included in the study

In all patients diagnosis of McArdle disease was achieved by means of histochemical, biochemical and/or genetic analyses

Results

Clinical Aspects

The clinical features of the 22 patients are summarized in Table 1.

The onset of symptoms ranged from 5 to 75 years old (7 pts in the first decade)

Presenting clinical manifestations were: massive rhabdomyolysis with myoglobinuria (2 pts), easy fatigability + exercise intolerance (14 pts), myalgia + muscle weakness at lower limbs (2 pts), presymptomatic hyperckemia (4 pts).

Several episodes of myoglobinuria (6/22)

Biochemical, morphological and genetic data

Serum CK was persistently elevated also, even at rest, in all patients (range 279 UI/L – 9589 UI/L).

EMG: myopathic pattern in 9 patients, unremarkable in the others.

Forearm ischemic test performed in 9/22: no lactate rise.

Muscle biopsy performed in 20/22: absence of phosphorylase staining in all patients but one. A mild glycogen storage found in all cases.

Residual enzymatic activity of phosphorylase: virtually absent in all pts examined

Molecular genetic analysis confirmed the diagnosis in all but three patients. Most common mutation: R50X (present in 45% of pts)

Table 1. Clinical and laboratory features in 22 McArdle patients

Pt/age/sex	Age at onset	Symptoms at onset	N° of episodes mioglobinuria	CK at rest (U/L)	EMG	Forearm ischemic test	Muscle biopsy	Muscle Myophosphorylase activity	PGYM mutations
1/66/F	50	myalgia, exercise intolerance	0	880	N	NP	myofibers variability, mild glycogen storage, absent PPL reaction	0,01	R50X/R50/X
2/7/M	6	myalgia, exercise intolerance	0	1191	N	NP	myofibers variability, mild glycogen storage, absent PPL reaction	0	R50X/L587P
3/21/M	15	rhabdomyolysis	4	1429	NP	NP	myofibers variability, mild glycogen storage, absent PPL reaction	0,01	c.148C>T/c.2262del A
4/19/F	5	myalgia, exercise intolerance	0	305	Myopathic	no lactate rise	myofibers variability, mild glycogen storage, absent PPL reaction	0,02	no mut gene
5/56/M	5	myalgia, exercise intolerance	2	731	N	no lactate rise	myofibers variability, mild glycogen storage, absent PPL reaction	0	no mut gene
6/28/M	23	myalgia, exercise intolerance	3	3036	N	no lactate rise	myofibers variability, mild glycogen storage, normal PPL reaction	0	753delA/753delA
7/22/F	5 circa	myalgia, exercise intolerance	0	800	N	no lactate rise	myofibers variability, mild glycogen storage, absent PPL reaction	0	R50X/R50X
8/18/M	15	myalgia, exercise intolerance	1	700	N	no lactate rise	myofibers variability, mild glycogen storage, absent PPL reaction	0,001	A364E/R575X
9/16/F	16	exercise intolerance	0	447	N	no lactate rise	myofibers variability, mild glycogen storage, absent PPL reaction	0,01	R50X/K754NfsX49
10/13/F	13	hyperckemia	0	4000	N	NP	np	np	R50X/K754NfsX49
11/75/M	75	hyperckemia	0	279	Myopathic	NP	myofibers variability, mild glycogen storage, absent PPL reaction	0	R50X/R50/X
12/50/M	40	hyperckemia	0	450	Myopathic	NP	myofibers variability, mild glycogen storage, absent PPL reaction	0,01	C-Het delGG esone 17/-
13/33/M	23	exercise intolerance	0	1002	N	no lactate rise	myofibers variability, mild glycogen storage, absent PPL reaction	0	R50X/IVS10 +1g>t
14/21/M	5	myalgia, exercise intolerance	1	9589	N	no lactate rise	myofibers variability, mild glycogen storage, absent PPL reaction	0	R50X/R50/X
15/9/F	5	myalgia, exercise intolerance	0	996	Myopathic	NP	myofibers variability, mild glycogen storage, absent PPL reaction	0,01	L587P/K754Nfsx49
16/53/F	30	myalgia, exercise intolerance, LGMW	0	642	Myopathic	NP	myofibers variability, mild glycogen storage, absent PPL reaction	0,02	c. 2178 +1G>A/ c.1275delG
17/50/M	48	myalgia, exercise intolerance	0	1643	N	NP	np	np	c. 2178 +1G>A/ c.1275delG
18/6/M	6	myalgia, exercise intolerance	0	4120	N	NP	myofibers variability, mild glycogen storage, absent PPL reaction	0,02	c.148C>T/c.2113_2114delCC
19/60/M	62	hyperckemia	0	1320	Myopathic	N	myofibers variability, mild glycogen storage, absent PPL reaction	0	no mut gene
20/41/F	5	myalgia, exercise intolerance	0	408	N	NP	myofibers variability, mild glycogen storage, absent PPL reaction	0,02	R93W/753delA
21/10/M	10	rhabdomyolysis	1	6826	Myopathic	NP	myofibers variability, mild glycogen storage, absent PPL reaction	0	R50X/R50/X
22/69/F	50	exercise intolerance, weakness	0	700	Myopathic	no lactate rise	myofibers variability, mild glycogen storage, absent PPL reaction	0.001	R50X/753delA

DISCUSSION

- **All McArdle patients showed a classical phenotype. The age at onset was variable: in 7/22 was in the first decade. The most common symptoms were myalgia and exercise intolerance. Only 2/22 at onset manifested with episodes of massive rhabdomyolysis. 4/22 patients were asymptomatic and were diagnosed because hyperckemia and/or because positive family history (2/4).**
- **Histochemical and biochemical analysis allowed us to define all the diagnoses.**
- **Conventional molecular genetic analysis (by direct sequencing of the entire coding region) failed to identified PYGM pathogenic mutations in three patients.**
- **A complete clinical and molecular characterization of patients with McArdle disease is today relevant because it will allow to identify selected subgroups of patients, likely available for new therapeutic trials.**

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