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Hypogammaglobulinemia in McArdle Myopathy (Glycogenosis Type V)

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Summary. Glycogenosis type V (McArdle) was the first myopathy to be enzymatically defined myopathy and has been found in approximately 120 patients. It is characterized by a myophosphorylase defect. In 2 patients with completely missing phosphorylase activity, muscle fiber necrosis and creatinine kinase elevation, we found reproducibly low gammaglobulins and low immunoglobulin-G. Compared with 124 nonmyopathic control patients with hypogammaglobulinemia, we did not find any established cause for low gammaglobulins in either case of McArdle disease. Myopathies with selected laboratory features or histopathology in common did not show changes in gammaglobulins or immunoglobulins. Unaffected family members had normal gamma-globulins and immunoglobulins. Therefore, gammaglobulins indicate an immunologic involvement in phosphorylase deficiency, and a potential for genomic co-localization.

Key words: Glycogen storage disease type V – Hypogammaglobulinemia – Immunodeficiency syndromes – Muscles/pathology

Introduction

The first enzymatically defined metabolic myopathy, glycogenosis type V, is characterized by myophosphorylase deficiency, abnormal glycogen storage, and muscle pain after isometric contractions. Out of 112 cases of McArdle's disease collected in the literature [2], 25% had residual enzyme activities, and 50% developed myoglobinuria; 51 of 97 McArdle patients had a positive family history. We followed two patients with missing myophosphorylase, without concomitant disease and in good health immunologically. In both we found significant and reproducible hypogammaglobulins and low immunoglobulin-G levels. We compared these findings with those in ten other myopathies, in 4 patients after extensive electromyography, and in 124 hypogammaglobulinemic patients without myopathy.

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Methods

Myophosphorylase-deficient patients showed myopathic EMGs, absent phosphorylase a + b activities, and no lactate elevation above normal yet intact ammonia responses to ischemia. Serum Na, K, Cl, Ca, PO_4, fasting glucose, uric acid, BUN, creatinine, alkaline and acid phosphatase, bilirubin, TT, PTT, amylase, lipase, $T_{3/4}$/TSH, CRP, ESR < 10/30 mm were within normal ranges, and rheumatoid factor, TPHA, borrelia IFT, influenza-A, coxsackie-B, HIV-1/2 and anti-DNA antibodies were negative in all patients unless otherwise indicated. Lymphocyte subtyping included CD3/4/8 (T cells), Leu7/ CD16/ NKH1 (killer cells), CD25/ CB1/ Ta1 (T cell activation) and T10 plus HLA-DR. Total B cells were calculated as leukocytes × lymphocytes-% × CD20-positive Ficoll cells. Hypothyreoid myopathy was excluded as described elsewhere [3]. Controls included (a) 80 male and 44 female patients with non-myopathic hypogammaglobulinemias, (b) 4 non-myopathic patients who had undergone repeated and detailed electromyographies, and (c) 10 patients with other muscle diseases. The gammaglobulin ratio GNG% was defined as the ratio between electrophoretic gammaglobulin versus nongammaglobulins (× 100).

Results

By 3 days, 7 days, 2 weeks and 5 weeks after extensive electromyography, four patients without myopathy had not developed significant changes in relative or absolute serum gammaglobulin or immunoglobulins. Reproducibly for a period of more than 6 months, however, the two McArdle patients displayed mean hypogammaglobulinemia levels of 8.8 g/l or 4.9 g/l respectively. Their mean GNG (gammaglobulin to non-gammaglobulin) ratios were 50% and 38%, markedly below both mean and median for 124 comparative hypogammaglobulinemic patients

Table 1. Absolute and relative hypogammaglobulinemia in McArdle myopathy

Patient number	1	2	3	4	5	6	CTRL
Mean γ-globulin g/l	**8.8**	**4.9**	12.5	12.6	10.6	13.7	8.0
Mean GNG* ratio %	**49.7**	**37.6**	77.6	87.8	73.6	83.6	55.5
Mean lymphocytes g/l	2.0	0.8	1.7	2.4	2.1	1.6	2.0
CK elevated to twice normal	+	+	+	+	+	Normal	Normal
Maximal CK-MB (% CK)	*30*	3.4	9.2	*22*	4	3	<
S-Aldolase > 7.6 units/l	+	+	−	Normal	Normal	Normal	Normal
S-Myoglobin > 85 µg/l	+	+	−	−	+	−	Normal

1, McArdle (25 years); 2, McArdle (62 years); 3, phosphofruktokinase deficiency; 4, lipid deposit myopathy; 5, alpha-1,4-glucosidase deficiency (M. Pompe); 6, polymyositis/collagenosis; CTRL, 124 non-myopathic patients with secondary hypogammaglobulinemia *GNG ratio = (gammaglobulins ./. non-gammaglobulins) × 100%

without myopathy (Table 1). Alternative causes for secondary hypogammaglobulinemia, such as recurrent infections, malignancies, trauma, surgery, empyema, renal insufficiency, colenteritis, hepatitis non-A, severe malabsorption, acitve autoimmune diseases, treatment with immunosuppressant agents, phenytoin or corticosteroids, were excluded, as were potential causes such as hemarthrosis, hydrarthrosis or bone cyst formation. Gammaglutamyl transpeptidase activities on admission were 6–6 units/l and 10–15 units/l.

McArdle Case 1

A 25-year-old housewife with proximal weakness and exercise-induced pain since childhood, slight obstructive-restrictive ventilatory impairment, sinus node arrhythmia, and elevated levels of creatine kinase (CK, 4-fold), aldolase (2- to 3-fold) and morning serum myoglobin (2- to 3-fold). Unremarkable lymphocyte subpopulations, no myoglobinuria, low normal functional immunoglobulins IgG, IgA, and IgM. Serum gammaglobulins 8.3–9.3 g/l, gammaglobulin to non-gammaglobulin ratio GNG = 43.7–55.7%.

McArdle Case 2

A 62-year-old carpenter with exercise-induced proximal pain, first noted at the age of 40–45 years, massive CK and serum myoglobin elevations (7- to 70-fold), aldolase elevated 3- to 4-fold, reproducible myoglobinuria. Low quantitative IgG (574–614 mg/dl), low to normal IgM (71.3–73.4 mg/dl) and normal serum IgA (150–304 mg/dl). Gammaglobulins with 4.5–5.3 g/l reduced to half lower limits, GNG ratio with 35.7–39.9% to below the 25th percentile of control hypogammaglobulinemias. Both his 65-year-old sister and his 70-year-old brother were not affected; their gammaglobulins and GNG ratios ranged around normal values. The patients's peripheral lymphocytes were low (0.8 g/l) compared with all others (median 1.8 g/l); he, in fact, reached the 5th percentile of 62 comparative non-myopathic hypogammaglobulin patients; simultaneously, his B cell percentage was not reduced (5% CD-20 positive cells). He showed no signs of T cell activation or T cell disproportionality; HLA-DR-positive cells accounted for 11% of circulating lymphocytes.

Four pathophysiologically related myopathies shared with McArdle's disease either lactate kinetics, myofibrillary degeneration, abnormal glycogen storage, or monohistiocytic infiltrates. Without exception, their gammaglobulins and GNG ratios were normal, with a mean gammaglobulin level of 12.9 g/l, and an average GNG ratio of 82.0% (Table 1).

Phosphofructokinase Deficiency Case 3

A 33-year-old man with 3-fold CK elevation, missing lactate response, and borderline CK-MB isoenzyme of 5.5–9.2% (16–20 units/l).

Lipid Storage Myopathy Case 4

A 46-year-old woman with muscle weakness for 18 years, myofibrillary degeneration, homogenous glycogen deposits and medium-sized lipid droplets within type-II fibers, and slightly increased CK-MB of 7.9–22% (14.4–96 units/l).

Glycogenosis II Pompe Case 5

A 47-year-old mother of three healthy children, proximal weakness for 10 years, constant liver enzyme elevation after hepatitis A and hepatitis B (gGT-SGOT/SGPT around 70 – 20/30 units/l); histomorphologically patchy and multifocal degeneration, CK-MB 3–9 units/l.

Polymyositis Case 6

A 63-year-old woman with uncharacterized collagenosis, muscle weakness for 6 months, accelerated erythrocyte sedimentation rate of 50/80 mm which normalized in the course of corticoid treatment, rather elevated gammaglobulins of 10.4–16.1 g/l, GNG ratio 73–92%. Interstitial lymphomonocytic myositis under light and electron microscope. Ultrastructurally, patches of mitochondria with strikingly variable size and form were seen, without identifiable cristae.

Cardiac biopsy to prove involvement of both striated muscle type phosphorylase and hybrid cardiac phosphorylase in patients with CK-MB elevations, i.e. McArdle and lipid storage myopathy (see Table 1) was not performed. Echocardiograms were normal and electrocardiograms yielded a sinus node arrhythmia in our female McArdle patient.

In six pathophysiologically less closely related muscular diseases, we found normal serum electrophoreses and lymphocyte counts. Mean gammaglobulin on admission measured 11.8 g/l, absolute values were: 13.3 g/l in nutritoxic myopathy (*1937), 13.1 g/l in muscle fiber necrosis following excessive exercise in anorexia (*1960), 12.5 and 9.6 g/l in two sisters with juvenile spinal myatrophy Wohlfahrt-Kugelberg-Welander (*1951) and (*1955), 11.6 g/l in a stout metal worker with slightly elevated 1:20 antistriated muscle antibodies (*1937), and 10.6 g/l in polymyositis without interstitial infiltrates (*1920) with antinuclear, antistriated muscle and low-titered anti-acetylcholine receptor antibodies.

Discussion

Humoral immunologic disorders have not been described in myophosphorylase deficiency [2, 6]. We found reproducibly reduced gammaglobulins and low immunoglobulin-G in both our patients with typical McArdle's disease, i.e. unmeasurable phosphorylase a and b activities. Their gammaglobulin to non-gammaglobulin ratio was decreased by 50%, indicating a selected hyposynthesis or hyperkatabolism of immunoglobulin-related polypeptides. Two decades after the onset of symptoms, both patients demonstrated constant creatine kinase, aldolase and myoglobin elevations. Whether hypogammaglobulinemia correlates to myoglobinuria as the expression of more extensive fiber necrosis or to sex-specific muscular metabolism is not commented on in the literature available. Pathophysiologically comparable myopathies with similar lactate response, myofibrillary degeneration, glycogen storage or monocytic infiltrates, however, did not show any humoral changes. Non-myopathic patients did not demonstrate reduced gammaglobulins, immunoglobulins or GNG ratios after repeated electromyographic examination. Whether relatively low total circulating B cells of 4×10^7/l in our older male patient correspond to severity of the disease, necessitates further observation. The myophosphorylase enzyme is restricted to muscle, heart and possibly brain tissue, but is absent in leukocytes [2].

Transitions from systemic lupus erythematosus (SLE) to so-called "common variable immunodeficiency," with IgG levels below 500 mg/dl, have been described [1]; despite extreme hypogammaglobulinemia, 4 out of 6 patients still had positive antinuclear antibodies. Transitions from glycogen storage diseases to humoral immunodeficiency syndromes are unknown. In contrast to some of the SLE patients, none of our patients with McArdle myopathy ever received immunosuppressives or phenytoin. Still, a random association of hypogammaglobulinemia and McArdle disease twice by chance cannot be completely ruled out, although the odds should be less than 1:50000. Chromosomal mapping of the defective myophosphorylase gene has not been reported. In man, the two light chain and five heavy chain type genes are so multi-allelic in inheritance that a topical colocalization of myophosphorylase with known immunoglobulin genes remains an intriguing possibility.

In secondary partial hypogammaglobulinemia, the differentiation between IgM or IgG specific B cells and secreting plasma cells seems impaired [8]. Polypeptides such as interleukin-4 are able to delay this differentiation [5]. Do myocellular cytotropic substances, particularly those liberated in McArdle muscle fiber necrosis, lead to an alteration of gammaglobulin metabolism? The only variant of hypogammaglobulinemia associated with muscle pathology we found was post-traumatic myositis ossificans accompanied by reversible hypogammaglobulinemia around 7.5 g/l; calcifications were not observed in McArdle myopathy. Acute ethanol impact, which causes ultrastructural myopathy and an elevated CK after consumption of 225–260 g ethanol daily for 3 weeks in previously healthy volunteers [7], could be ruled out. Chronic alcohol ingestion, as reported elsewhere [9], needs very high cumulative doses of 13 kg ethanol/kg body weight to cause measurable non-cardiac myopathy. Even a low-dose dependency was more than unlikely in our two patients.

Half the patients with McArdle myopathy reported in literature had a positive family history. In all brothers and sisters of our patients, gammaglobulins and immunoglobulins were congruent with the clinical muscular state, i.e., normal. If an association between lacking myophosphorylase and altered gammaglobulin metabolism could be confirmed, simple serum analyses would offer additional serologic parameters for this rare metabolic disorder characterized 30 years ago. Since patients with late-onset hypogammaglobulinemia without lymphoproliferative disease run an increased risk of gastric cancer [4], we have recommended a thorough follow-up for both McArdle patients in this respect.

In conclusion, we ask for a complete history of infectious diseases, for serum electrophoresis and quantitative immunoglobulins in patients with suspected or confirmed metabolic myopathy.

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Note added in proof. In our McArdle patients, myophosphorylase protein could not be detected in biopsy material. Of comparable patients without residual activity or enzyme protein, Martinuzzi now reports intact and functional myophosphorylase recovery after innervated in-vitro muscle culture, arguing for a transcriptional or translational defect rather than an enzyme gene deficiency. (Martinuzzi A et al. (1990) J Neurol Sci 98:S60)