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Serum interleukin 15 levels in patients with seropositive myasthenia gravis do not correlate with disease severity

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ABSTRACT

Aim: To assess interleukin 15 (IL-15) serum levels in patients with seropositive myasthenia gravis (MG); searching for potential relationship between IL-15 levels and clinical features such as gender, age at onset, clinical presentation or treatment received.

Background: IL-15 plays pivotal role in T-cell dependent autoimmunity. Increased IL-15 serum levels have been reported in several autoimmune diseases including MG patients from Japan.

Patients and methods: Sera of 42 seropositive MG patients (66.7% women), mean age 50.6 ± 23.7 years) have been tested by ELISA for IL-15 levels.

Results: There were no statistically significant differences between IL-15 serum levels in MG patients in comparison with controls as well as between subgroups of MG patients (early vs. late onset and thymoma MG). Mean/median IL-15 serum levels were similar in MG patients treated with corticosteroids (CS) and CS naïve. Outliers (very high values) were seen only in untreated generalized MG patients.

Conclusions: Serum interleukin 15 levels in patients with seropositive myasthenia gravis do not correlate with disease severity.

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1. Introduction

Myasthenia gravis (MG) is a neuromuscular disease caused in 80–95% of patients by a T-cell dependent autoantibody response against receptor for acetylcholine at the postsynaptic

muscle membrane (AChRab). AChRab in the neuromuscular junction cause neuromuscular transmission disturbances and, as a consequence, muscle weakness and fatigability. AChRab serum levels show no correlation with the severity of MG course and no biological marker of MG severity was identified so far [1]. Also factors active in triggering and

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sustaining the autoimmune reaction in MG are unknown. Studies in experimental MG (EAMG) suggested that myocytes are not only passive participants or target of the immunologic cascade, but are active during the course of the disease by producing specific cytokines, including interleukin 15 (IL-15) [2,3]. IL-15 stimulates interferon gamma (INF gamma) production. INF gamma in turn was proved to enhance experimental MG symptoms [2,4–6]. IL-15 not only induces T lymphocytes proliferation, enhances NK cells cytotoxicity and leads to increased production of their cytokines and chemokines, but also facilitates survival of CD8+ memory T cells including self-reactive memory T-cells [7].

Increased IL-15 serum levels have been reported in several autoimmune diseases, including systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, diabetes type 1 or celiac disease [7,8]. Increased serum IL-15 levels were reported in Japanese MG patients not treated with immunosuppressants or thymectomy [8]. It prompted us to verify the hypothesis that IL-15 serum level is increased in a group of Caucasian seropositive MG patients and test its possible relationship with clinical features such as gender, age of onset, clinical presentation or treatment received.

2. Patients and methods

2.1. Subjects

42 patients with seropositive MG were enrolled in this study in the period between 2011 and 2014 after informed consent. Clinical diagnosis of MG was confirmed by positive result of repetitive nerve stimulation test or single-fibre electromyography (SFEMG) and elevated serum anti-AChR levels. 66.7% of tested patients were women; age of onset ranged from 15 to 85 years (mean 50.6 ± 23.7 years). By definition all subjects had seropositive MG. 42.9% of patients were classified as early onset MG (EOMG, <50 years), 45.2% as late onset MG (LOMG, ≥ 50 years); 11.9% had thymoma-MG (T-MG). The majority (78.6%) of the subjects were never treated with corticosteroids (CS) or other immunosuppressants. 19% of all patients underwent thymectomy. In 14.3% of the patients autoimmune thyroid disease coexisted with MG. The severity of symptoms was assessed according to Myasthenia Gravis Foundation of America (MGFA) clinical classification scale. 88.1% of subjects had generalized MG. Two patients (4.8%) were in complete stable remission. Sera of 16 subjects with no history of MG or other autoimmune diseases served as normal controls. All sera were frozen and stored at -73°C until analysis.

2.2. Methods

IL-15 serum levels were measured by ELISA (BioLegend IL-15 Pre-coated ELISA Kit, according to the manufacturer's instruction, by MD). The detection limit of ELISA Kit was 2 pg/ml.

2.3. Statistical analysis

Independent-Samples T test, after Levene's Test for Equality of Variances and U Mann Whitney test, were used to compare

respectively means and ranges of IL-15 serum levels within groups taken into comparison. Correlations between IL-15 and AChRab serum levels and clinical and laboratory features were studied using Pearson's and Spearman's tests, as appropriate. Statistical significance was defined at $p < 0.05$.

3. Results

There was no significant difference between serum IL-15 levels in patients with MG as compared to controls (9.87 ± 9.37 (median 7.38; $Q1 = 4.51$, $Q3 = 10.28$) vs. 8.69 ± 3.61 pg/ml (median 8.69; $Q1 = 5.13$, $Q3 = 11.38$), respectively; $p = 0.449$). There was also no significant difference between women and men (9.29 ± 7.79 (median 7.38; $Q1 = 4.62$, $Q3 = 9.43$) vs. 11.21 ± 12.64 pg/ml (median 6.81; $Q1 = 4.28$, $Q3 = 11.31$); $p = 0.560$). Also the patients treated with corticosteroids within the last 3 months did not have lower IL-15 serum levels than patients who have received prednisone recently (7.67 ± 4.17 (median 8.02; $Q1 = 4.04$, $Q3 = 11.31$) vs. 10.19 ± 10.05 pg/ml (median 7.05; $Q1 = 4.52$, $Q3 = 10.35$), respectively; $p = 0.941$); there was also no differences in IL-15 levels in patients treated with corticosteroids in the past vs. untreated (Fig. 1).

Patients with generalized MG had similar mean serum IL-15 levels as patients with ocular MG only (9.92 ± 9.85 (median 6.67; $Q1 = 4.48$, $Q3 = 10.52$) vs. 8.45 ± 4.45 (median 8.97; $Q1 = 4.72$, $Q3 = 11.92$); $p = 0.641$) (Fig. 2). Patients with EOMG tended to have lower IL-15 serum levels from LOMG (8.53 ± 5.41 (median 6.62; $Q1 = 4.58$, $Q3 = 10.89$) vs. 11.65 ± 12.87 (median 8.07; $Q1 = 4.33$, $Q3 = 11.66$); $p = 0.380$) (Fig. 3). There were similar serum IL-15 levels in T-MG in comparison with other MG groups (9.25 ± 3.46 (median 8.59; $Q1 = 6.17$, $Q3 = 13.00$) vs. 9.71 ± 9.66 ; $p = 0.936$ (median 8.07; $Q1 = 4.33$, $Q3 = 11.66$), respectively). We have not found significant differences between patients with or without autoimmune thyroid disease (respectively 8.61 ± 2.96 (median 7.05; $Q1 = 4.47$, $Q3 = 10.05$) vs. 9.86 ± 10.03 ; (median 6.72; $Q1 = 4.47$, $Q3 = 10.75$) $p = 0.283$).

One patient had IL15 level below detection limit.

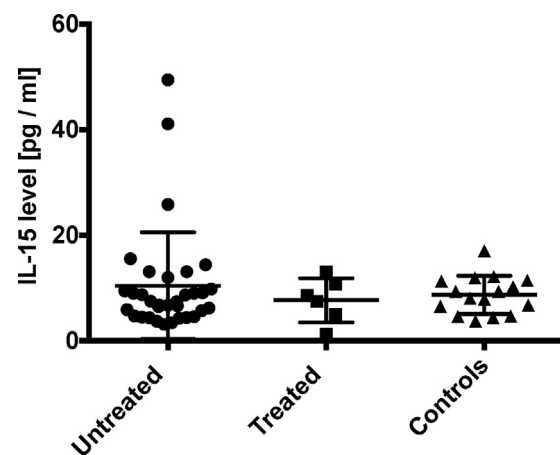


Fig. 1 – IL-15 serum levels in patients untreated vs. treated with corticosteroids (CS) within last 3 months. Patients treated with CS tend to have lower IL-15 serum levels (p ns).

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