Vaccinations in autoimmune myasthenia gravis

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Chapter 2

Presence of AChR antibodies before clinical onset myasthenia gravis

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1. INTRODUCTUION

Myasthenia Gravis is a disorder of the neuromuscular junction characterized by fluctuating muscle weakness influenced by exercise. The onset of auto-immune myasthenia and evolution in the individual patient has a variable pattern and the diagnosis is often made in the second year after symptom onset [1]. All voluntary muscles may be involved, but many patients start with ocular symptoms like double vision and drooping eyelids. Antibodies to the acetylcholine receptors (anti-AChR) on the muscle membrane [2] are the antibodies that are most frequently found. Finding these antibodies is highly specific (>99%) for the diagnosis whereas the sensitivity of the test is usually around 85% [3, 4]. In seronegative patients or in case a rapid diagnosis is mandatory, neurophysiologic tests may be helpful [5]. Anti-AChR antibodies are not a reliable biomarker for the clinical severity or the clinical change at group level, but can show a reasonably good correlation in one and the same patient [6]. Although there is conclusive evidence that the anti-AChR antibodies are pathogenic [7, 8], it is unknown what triggers the start of the anti-AChR immune response and how long seroconversion may precede clinical symptoms. Prospective monitoring of the onset of anti-AChR antibodies in a group of individuals at risk for MG would be helpful, but is not feasible due to the low incidence of the disease.

We encountered a unique case of a young female with MG in whom serum samples were available over a period of at least 2 years before the onset of clinical symptoms. We studied the anti-AChR levels before onset of clinical symptoms and during treatment in the years thereafter.

2. CASE REPORT

A 22 years-old female experienced symptoms of unspecific fatigue, muscle pain and arthralgia after her first pregnancy in 1986. She was surmised from having an auto-immune disease and thus seen by an experienced immunologist. Although a-specific symptoms of fatigue and arthralgia were reported, no rheumatic arthritis and SLE associated antibodies could be found and no diagnosis could be made for the time being. A wait and see policy was followed and the patient consented to participate in an SLE research programme for which blood samples were collected and stored at regular intervals. By the end of 1988 she got pregnant for the second time and delivered in august 1989. Her new-born daughter experienced problems with drinking, for which she was fed through a tube, and had a feeble cry during the first days after birth. In retrospect, she might have been suffering from neonatal myasthenia gravis. The day after delivery the patient herself developed swallowing problems, dysarthria, loss of strength in her hands and weakness in the neck muscles. By then, the diagnosis of MG was made based on clinical symptoms and repetitive nerve stimulation (decrement 17% in the ulnar muscles). She was treated successfully with anticholinesterases. Anti-AChR serum antibodies were found positive one week later (68 nmol/l; normal values <1 nmol/l (9)).

Being asked for specifically she remembered periods of a tired feeling of the eyelids by watching television in February 1989 after 3 months of pregnancy. She experienced no other clinical symptoms, suspect for myasthenia. Although she was interviewed on a regular base, her rheumatologist, being a specialist in auto-immune diseases, did not recognize her eyelid symptoms as being abnormal and did not notice other symptoms that would suggest a clinical diagnosis of MG.

Serum samples, collected in the two years before the apparent symptoms, were analysed for anti-AChR antibodies. The first sample in 1986 showed a titer of 13 nmol/l and there was a gradual increase towards 82 nmol by the end of her pregnancy 2.5 years later, without any clinical suspicion of myasthenia. In retrospect, at time of the first symptoms of 'tired eyelids' the serum level was 48 nmol/l.

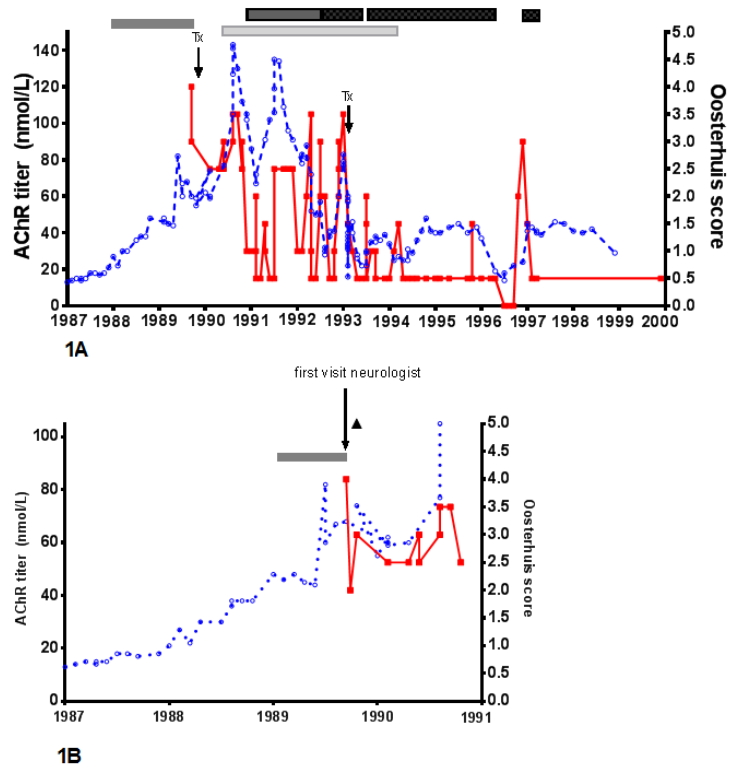

Figure 1A: Course of anti-AChR antibodies, clinical score and medication over a period of 13 years. Oosterhuis score: 0 remission, no medication use, 1 minimal signs and symptoms, 2 mildly disabled, 3 moderately disabled, 4 severely disabled, 5 respiratory support needed. Anti-AChR antibodies (), Oosterhuis score (), thymectomy (Tx), Pregnancy (), Azathioprine dose of 50-150mg/day(), Cyclosporine dose of 100-400mg/day (), mean daily prednisolone dose of 5-60mg/day (). **1B:** Enlargement of course during the first 4 years.

She was followed clinically until she went into clinical remission of myasthenia after intensive medical and surgical treatments: in 1990, half a year after delivery she underwent a thymectomy, later on was treated with prednisolone, azathioprine and cyclosporine. In 1993 she underwent another 'extended' thymectomy, at which some thymic remnants were found. Hereafter, the MG seemed to be milder with occasionally a mild upbeat of symptoms that could be treated with increasing the cyclosporine or adding some steroids. Another three years later, in 1996, the diagnosis of SLE was made based on positive ANA, anti-dsDNA, pleuritis, cutaneous manifestations, renal disorder and joint disease and for this, immunosuppressive therapy was intensified. Myasthenic symptoms subsided and no further antibody-titers were determined from the end of 1998. A survey over clinical course, therapies and antibody-titers is depicted in figure 1a and an enlargement of the course in the beginning years is depicted in figure 1b. The patient died in 2012 at the age of 47 years because of complications of the SLE.

3. DISCUSSION

This patient showed a gradual increase of anti-AChR antibodies in a period of more than two years before becoming symptomatic of myasthenia. Over these years she was followed by an experienced immunologist, being familiar with myasthenia gravis, who did not recognize any suspect symptom for this disease.

Pregnancy is a well-known trigger for the clinical onset of MG, and there is a considerable risk for clinical onset during the post-partum period [10]. Myasthenia might be associated with other auto-immune disease like rheumatic arthritis and SLE and a puerperal onset of this disease has been described as well [11]. To the best of our knowledge there is no description of a long course of anti-AChR titers before the onset of myasthenia but the presence of autoantibodies several years before clinical symptoms appeared has been described in inflammatory arthritis [12].

During the more than 10-year follow-up period in this patient anti-AChR antibody titers significantly correlated with the Oosterhuis score [13] (Spearman rank correlation coefficient: $r=0.52$; $p<0.0001$). That this correlation is only 'reasonable' [6] is obvious: at several time points in the symptomatic period of the study, anti-AChR titers were at the same level as before onset of clinical symptoms. This stresses the complex relationship between anti-AChR antibodies and disease severity, even in an individual patient.

In conclusion, anti-AChR antibodies can be present at least two years before patients experience overt clinical symptoms of MG. The data suggest that in our patient pregnancy triggered the clinical manifestation of a smouldering autoimmune antibody response, but is not the primary trigger in itself.

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