

Spontaneous remission in canine myasthenia gravis: Implications for assessing human MG therapies

Article abstract—The natural course of autoimmune canine MG was determined in 53 dogs with muscular weakness and a positive acetylcholine receptor antibody titer. Dogs were treated with anticholinesterase therapy, without immunosuppression. Spontaneous clinical and immunologic remission occurred in 47 of 53 dogs within an average of 6.4 months. Neoplasia was identified in the six dogs that did not spontaneously remit. This study questions the value of using canine MG in studies designed to assess the effect of immunotherapies.

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Acquired MG is probably the most common neuromuscular disease that can be diagnosed in dogs and is very similar to human MG, including the epitope specificities of the predominant autoantibodies.^{1,2} Given this similarity, the dog is a good animal model for studying human MG and testing new therapeutic modalities. Because spontaneous remissions have been reported in the dog,^{2,3} the natural course of the disease should be defined before initiation of therapeutic trials.

A recent report described the inadequacy of clinical trials in human MG without evidence-based data on optimum treatment regimens.⁴ Guidelines have recently been proposed for well-designed therapeutic trials.⁵ This study was performed to establish the natural course of canine MG in the absence of immunosuppression and to provide guidelines for therapeutic trials using the spontaneous canine model of MG.

Methods and materials. Dogs diagnosed with immune-mediated MG with positive acetylcholine receptor antibody titers (>0.6 nmol/L) by established radioimmunoassay¹ were studied. Only dogs that received no therapy modification of feeding procedures including elevation of food and water or placement of a gastric feeding tube, or anticholinesterase drugs were included. Dogs were excluded if they received corticosteroids or other immunosuppressive therapies. Clinical (pharmacologic) remission refers to resolution of clinical signs including muscle weakness and esophageal dilatation with the dog remaining on anticholinesterase therapy. Immune remission refers to the return of the AChR antibody titer to the reference range (<0.6 nmol/L) and to the dog as clinically normal in the absence of anticholinesterase therapy.

Results. Fifty-three dogs of several different breeds that were diagnosed with MG between 1990 and 2000 fulfilled

criteria for inclusion in this retrospective study. Dogs ranged in age from 7 months to 13 years at the time of diagnosis. Female dogs (intact = 7, spayed = 24) outnumbered males (intact = 5, neutered = 17). Clinical classifications included MG localized to only the esophageal or pharyngeal musculature (focal MG) in 15 of 53 (28.3%); generalized weakness involving esophageal and limb musculature (generalized MG) in 37 of 53 (69.8%); and acute, fulminating MG with rapid onset of severe generalized muscular weakness in 1 of 53 (1.9%) dogs. Time elapsed from onset of clinical signs until confirmation of diagnosis ranged from 1 week to 5 months. The AChR antibody titer was >0.6 nmol/L at the time of initial diagnosis in all cases (mean, 4.4 nmol/L; range, 0.9 to 11.1 nmol/L). Clinical remission was achieved in 47 of 53 dogs (88.7%) within an average of 4.1 months (range, 1 to 12 months). Immune remission was achieved in 47 of 53 dogs (88.7%) in an average of 6.4 months with a range of 1 to 18 months (figure 1). All 6 dogs (11.3%) that did not remit exhibited neoplasia diagnosed after the onset of MG: thymoma in 4 was diagnosed after 2 to 3 years, thyroglossal duct papillary cystadenocarcinoma in 1 was diagnosed after 1 year, and melanomasarcoma in 1 was diagnosed after 2 years.

Long-term follow-up was available for all 47 dogs that went into clinical and immune remission. Relapse of MG was not reported in 45 of 47 (95.7%) dogs, with the dogs clinically normal for periods ranging from 1 to 7 years. A possible relapse occurred in 2 of 47 dogs approximately 2 years after clinical and immune remission. One dog became symptomatic and its AChR antibody titer elevated following routine vaccination. The second dog was euthanatized without confirmation of the diagnosis. Nine more dogs were euthanatized for unrelated causes within 3 to 5 years following remission of MG. The remaining dogs (37/47) were still alive and clinically normal at the time of this writing.

Figure 2 shows sequential AChR antibody titers for one of the dogs with MG. The AChR antibody titer decreased dramatically in the first 2 months following diagnosis of MG. An ovariohysterectomy was performed 5 months after the diagnosis, when the dog was in clinical remission. One week following the surgical procedure, the dog again became weak, megaesophagus was radiographically apparent, and the AChR antibody titer had increased. Nine months after diagnosis, the dog was in clinical and immune remission. The dog remained asymptomatic until 24 months after the initial diagnosis. The dog was vaccinated, and again the AChR antibody titer increased and clinical weakness was apparent. Clinical and immune remission

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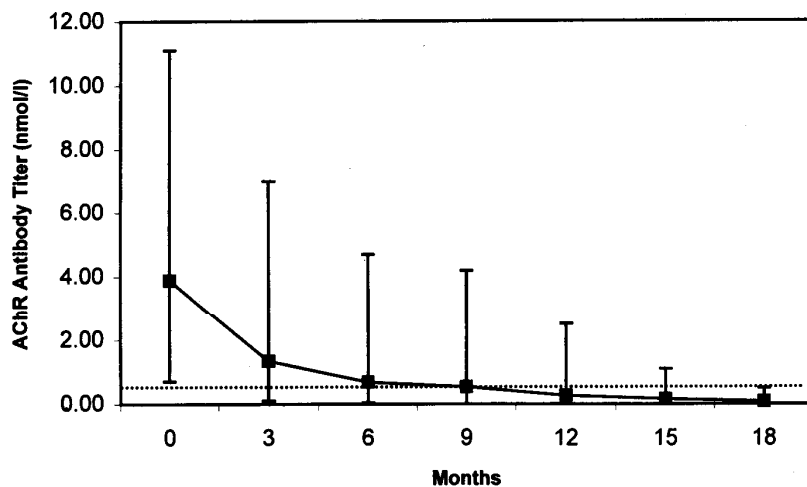


Figure 1. Time course of canine MG measuring sequential acetylcholine receptor (AChR) antibody titers in 47 dogs that experienced spontaneous clinical and immune remission. Shown are the average and range of antibody titers from the 47 dogs at time of confirmed diagnosis of MG (month 0) until all dogs achieved clinical and immune remission at 18 months. Dotted line = 0.6 nmol/L. An AChR antibody titer <0.6 nmol/L is consistent with immune remission.

was again achieved, and the dog has continued in both clinical and immune remission as of this writing (43 months following initial diagnosis).

Discussion. This study demonstrates the high rate of spontaneous remission in dogs with acquired MG and raises considerable doubts concerning the suitability of canine MG as a model for therapeutic trials for human MG. Equally, these observations draw attention to the importance of considering the natural course of human MG itself when evaluating the effectiveness of thymectomy and other therapeutic modalities over long intervals. The natural course of human MG is generally one of improvement or steady state after the first 1 to 3 years with rapidly declining mortality after this time.⁶ Similar to human MG, mortality in canine MG is highest in the first 2 months following diagnosis (Shelton, unpublished data, 2001). These findings are often ignored when considering responses to therapy.

Severity of MG did not appear to be a factor in whether remission was obtained or in the development of neoplasia (5/6 dogs had generalized MG, 1/5 dogs had focal MG). Surgical stress was associated

with worsening of MG in one dog (see figure 2), similar to that described in human patients.⁷ Vaccination coincided with reoccurrence of clinical MG and elevation of the AChR antibody titer (see figure 2). With the exception of the dog that underwent exacerbation of MG following surgery and reoccurrence of MG following vaccination, none of the dogs to date have had a reoccurrence of MG or increased AChR antibodies.

The rate of remission and loss of autoantibodies in canine MG (average time of 6.4 months) is similar to that in rheumatoid arthritis patients with MG induced by treatment with penicillamine (50% decrease in antibody titer in 35 to 60 days and remission in less than 6 months)⁸ and may reflect the rate at which the autoimmune response to AChR declines after the immunogen is removed. Penicillamine-induced MG is thought to be caused by haptenating the AChR through covalent reaction of the drug.⁹ The rapid sustained remission of canine MG may result from transient exposure to immunogen (e.g., clearing of an infection that resulted in presentation of AChR in an immunogenic context),

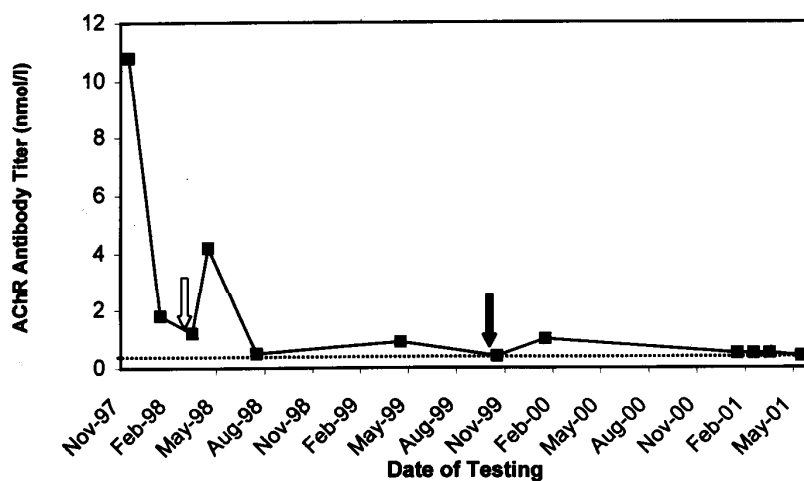


Figure 2. Sequential acetylcholine receptor (AChR) antibody titers from a 3-year-old female Scottish Terrier with generalized MG. Clinical weakness was exacerbated, and the AChR antibody titer increased following surgical ovari-hysterectomy (open arrow). Reoccurrence of clinical MG and an elevated AChR antibody titer occurred following vaccination (closed arrow), 15 months after clinical remission. Dotted line = 0.6 nmol/L. An AChR antibody titer <0.6 nmol/L has been established as the reference range.

whereas the more prolonged time course of human MG⁶ may result from sustained exposure to immunogen (e.g., a chronic infection that sustains the immune response through presentation of the AChR in an immunogenic context). The recovery exhibited after canine MG, human neonatal MG, and both passive and chronic experimental autoimmune MG illustrate that the immune stimulation from AChR released from neuromuscular junctions is insufficient to sustain a chronic autoimmune response.¹⁰

Canine autoimmune MG has many advantages for the study of human MG including the natural occurrence of the disease, the sharing of similar environments between humans and dogs, the similarities in clinical presentations, the presence of diagnostic AChR antibodies of similar epitope specificities, and the occurrence of MG with other autoimmune diseases. Canine MG is uniquely suited to study triggers of the aberrant autoimmune response and correction of this aberrant response in the absence of immunosuppression. If the canine model is used for study of specific therapies for MG, appropriate control groups must be included before any interpretation of data can be made and, given the relatively rapid fall in anti-AChR levels, it is doubtful whether such trials would show treatment benefit. This study further supports the recent article⁵ emphasizing appropriate, randomized, therapeutic trials not only in human MG patients but also in animal models.

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