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Case report

Congenital myasthenic syndrome due to mutation in CHRNE gene with clinical worsening and thymic hyperplasia attributed to association with autoimmune-myasthenia gravis

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Abstract

We report a patient with congenital myasthenic syndrome (CMS) due to mutation in CHRNE with symptoms since the age of 4; mild to moderate fatigable weakness involved mainly ocular, bulbar and limb muscles; functional impact of the disease in their development and physical activity was modest. By the age of 34, the patient experienced gradual worsening of fatigue with dyspnoea and pronounced limb weakness, requiring significant increase of pyridostigmine. Further, a remarkable and sustained clinical improvement followed thymectomy with hyperplastic thymus. Despite of the absence of detectable antibodies to acetyl-choline receptor (AChR) (including clustered-AChR), muscle-specific kinase and low-density lipoprotein receptor-related protein-4 antibodies in the serum obtained nine years after thymectomy, the clinical, genetic and histological features are in keeping with the extremely rare association of two rare neuromuscular junction disorders – CMS and myasthenia gravis (MG). The inexistence of other conditions that could potentially associate with thymic hyperplasia also supports the diagnosis of MG.

Keywords: Myasthenia gravis; Congenital myasthenic syndrome; Neuromuscular junction disorder

1. Background

The dysfunction or loss of acetylcholine receptors (AChR) in the neuromuscular junction may have different causes. The most frequent cause is autoimmune myasthenia gravis (MG), which is mostly caused by antibodies to AChR (AChR-MG). Less commonly the neuromuscular transmission defect is genetic – associated with mutations in a number of molecules expressed in the neuromuscular junction, including AChR subunits, clinically defined as congenital myasthenic syndromes (CMS). Here we report a patient with CMS due to mutation in CHRNE (AChR deficiency) with clinical manifestations since the age of 4, who developed MG with hyperplastic thymus by the age of 34 years. The patient gave informed consent, allowing the authors to report his case anonymously.

2. Case report

Two siblings of non-consanguineous healthy parents developed very similar neuromuscular manifestations by the age of 4 and 6 years respectively – progressive ophthalmoplegia, dysphonia, fatigable difficulty in chewing and fatigable weakness in the limb muscles. Electromyography with repetitive nerve stimulation showed significant decrement, suggestive of postsynaptic defect of neuromuscular transmission. Serum levels of muscle enzymes were normal. Muscle biopsy performed in the oldest brother showed subtle abnormalities, suggestive of myopathic origin. Genetic study revealed a mutation on the gene for the AChR epsilon subunit – CHRNE, confirming the diagnosis of CMS in both children. They were treated with pyridostigmine with significant improvement of their muscle strength to be able to practise some sports in school and to work as mechanics later in life.

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By the age of 34 years (2003), the oldest brother developed dyspnoea and worsening of the weakness in the limbs; pyridostigmine dose was increased from 240 mg to 600 mg per day with benefit. Electromyography with repetitive nerve stimulation showed significant decrement, 27%, in the amplitude of the compound muscle action potentials (CMAPs) on the facial nerve, right nasalis, and 40% on the right trapezium, again suggestive of post-synaptic defect of neuromuscular transmission. Chest CT scan showed a mediastinal mass and several mildly enlarged lymph nodes. Thymus was removed, and the histology revealed a hyperplastic thymus. The lymph nodes were found to be related to a thyroid papillary carcinoma. Thyroidectomy followed by radioactive iodine therapy was performed. Thyroid function was always normal.

Some months later he returned to his previous clinical and functional baseline; the dose of pyridostigmine was reduced back to the initial dose of 240 mg per day and he has remained stable ever since. Blood sample to test for autoantibodies associated with MG was only obtained in 2012, nine years after the thymectomy; antibodies to AChR (against the adult and foetal isoforms of the receptor and also to clustered-AChR), muscle specific kinase (MuSK) and low-density lipoprotein receptor-related protein-4 (LRP4) were negative. The second brother also tested negative for AChR, MuSK and LRP4 antibodies.

3. Discussion

3.1. Current case

In this case report we highlight the extremely rare association of two rare disorders affecting the neuromuscular junction, a congenital myasthenic syndrome with autoimmune myasthenia gravis associated with thymic hyperplasia.

Congenital myasthenic syndromes are rare inherited disorders that are associated with mutations in genes encoding molecules expressed in the neuromuscular junction and affect the neuromuscular transmission. CMS clinical and demographic features, including the age of presentation, neurological manifestations, their severity and response to treatments, do sometimes vary. Overall, their variability depends on the molecules and function affected. The most common CMS syndrome identified is associated with mutation in the CHRNE gene (AChR deficiency), especially in Mediterranean countries [1], the same that our patient and brother have. As in this family, it is usually an autosomal recessive syndrome which presents mainly in childhood, causes decrement in the RNS and responds to pyridostigmine, although sometimes incompletely [1].

Myasthenia gravis is an autoimmune disease, which may have a multifactorial underlying basis, particularly genetic and immunological. It is thought to be caused by a complex interaction between multiple genotypes of low penetrance and immunological and environmental factors. In early 80s Human Leukocyte Antigen (HLA) analyses led to determination that HLA-A1, B8 and/or DRw3 were the main risk alleles for the disease, especially for women, with early onset MG, AChR antibodies and hyperplastic thymus, whereas HLA-A3, B7 and DRw2 were associated with late onset MG with AChR antibodies, without thymoma and affecting particularly males [2]. Meanwhile, many other studies have been published on genetic factors in MG [3,4].

In around 85% of patients, MG is caused by autoantibodies directed to AChR, a pentameric molecular complex of four subunits, α2, β, δ and ε, in the adult. Knowing the central role of AChR in MG pathogenesis, genes encoding for these subunits were studied to understand the possible role of genetics in the development of the disease. Association and linkage of CHRNA1, the gene for α-subunit, with MG was demonstrated [5]. More recently, an association of the gene encoding the δ-subunit of the muscle acetylcholine receptor (CHRND) with acquired autoimmune myasthenia gravis was also described [6]. Mutations in these genes are also responsible for congenital myasthenic syndromes. Those studies strengthen the interest for the genes encoding self-antigens in the analyses of a genetic predisposition to autoimmune diseases.

It is extremely rare for both forms of neuromuscular transmission disorders (genetic and autoimmune myasthenia) to associate. Therefore, alternative explanations for the main clinical and histological findings were addressed and discussed. We wondered whether the worsening of myasthenia symptoms could be only related to the CMS. Although very rare in this particular mutation, patients may experience worsening of symptoms. They may be transient exacerbations, which are often triggered by clinical events such as infection or certain medications; in other patients, there may be gradual deterioration of the symptoms later in life, without eventual significant improvement [1]. Our patient did not have a transient exacerbation nor did he have a progressive irreversible worsening. After a period of unequivocal disease deterioration, his clinical manifestations improved to the baseline, and he has remained stable for over 10 years following thymectomy. One could also argue that thymic hyperplasia is not specific of MG. Thymic hyperplasia is a well recognised and strong biological marker of a subtype of MG (AChR antibody-mediated disease of early onset) [2,7] and, more rarely, can be found in MG cases seronegative for AChR and MuSK antibodies [7]. We acknowledge that thymic hyperplasia may be also found, occasionally, in patient with other autoimmune conditions such as systemic lupus erythematosus and thyrotoxicosis [8], none of which this patient had.

Overall, we could not find other unifying diagnosis for this patient's acquired condition, but MG with thymic hyperplasia; the negativity for the antibodies could be explained by the time between the development of MG symptoms and blood sample collection (nine years after thymectomy). Interestingly, one of the CMS siblings reported by Croxen et al. [9] also developed, later in life, MG with AChR antibodies, which became undetectable after thymectomy, which lends strength to our case report and emphasises its clinical relevance.

3.2. Myasthenia gravis in patients with genetic neuromuscular conditions: summary

To our knowledge, and apart from these two very similar cases (the one reported in 2002 by Croxen et al. [9] and our current patient), there have been no cases of co-existence of