

Co-existent Ocular Myasthenia Gravis and Graves' Disease in a 5-Year-Old

Dr. Olivia Watson¹, Associate Prof. Michelle Jack^{1,2},
Associate Prof. Helen Young^{1,2}

¹Paediatrics Department, Royal North Shore
Hospital, Reserve Rd, St Leonards NSW, Australia
2065

²Northern Clinical School, Sydney Medical School,
University of Sydney

ABSTRACT

Myasthenia gravis and Graves' disease are known to co-exist in adults, yet there have only been a small number of paediatric cases reported. We report a 5-year-old female who was diagnosed with ocular myasthenia gravis after presenting with unilateral ptosis and subsequently found also to have Graves' disease. She was treated successfully with pyridostigmine, corticosteroids and carbimazole without symptom recurrence or progression to generalised myasthenia gravis. The aetiology of the coexistence is not fully understood, nor is the relationship between the two disorders' presentation and treatment. We discuss the variation in the clinical presentation of myasthenia gravis with age, ethnicity and association with autoimmune thyroid disease; as well as potential HLA-related genetic susceptibility and the varying approaches to the treatment of the co-existent disorders.

Keywords: *Myasthenia gravis, Graves disease, thyroid disease, autoimmunity, paediatrics*

Introduction

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction leading to fatigable muscle weakness. Graves' disease is an autoimmune thyroid disease and the leading cause of hyperthyroidism in children. The association between MG and Graves' disease is well reported in adults, however, there have only been a small number of reported cases (1,2) in children. We report the case of a 5-year-old female diagnosed with coexistent ocular myasthenia gravis (OMG) and Graves' disease.

Case

A previously well 5-year-old girl of East Asian background presented with a two-week history of isolated left-sided ptosis, noted to be worse in the evenings. Her medical history was significant for extreme prematurity at 26 weeks but her development was appropriate for age. Her

only medications were vitamin supplements. There was no known family history of autoimmune disease.

She had had a mild upper respiratory illness 2 weeks preceding presentation and was otherwise well. On examination, there was left-sided ptosis with ocular muscle fatigability. The rest of her neurological examination was normal; in particular, there were no other features of Horner's syndrome or third cranial nerve palsy. A diagnosis of probable OMG was made. Full blood count, electrolytes, liver function tests, C reactive protein and erythrocyte sedimentation rate were normal. Acetylcholine receptor (AChR) antibodies were positive at 0.45nmol/L (normal range (NR) <0.25nmol/L, equivocal 0.25-0.4nmol/L, positive >0.4nmol/L), consistent with the diagnosis of MG. Muscle-specific kinase (MuSK) antibodies were negative. Brain MRI was normal other than small areas of gliosis in keeping with prematurity, and chest MRI to exclude thymoma was normal. Ocular single fibre electromyography (EMG) was not tolerated so not performed. EMG with repetitive stimulation in the right abductor digiti minimi and right tibialis anterior was normal, supporting the diagnosis of isolated OMG only. Oral pyridostigmine (up to 30mg four times per day) was commenced.

The ptosis and extraocular muscle weakness initially completely resolved with pyridostigmine therapy, however, after one month the unilateral ptosis returned with new divergent strabismus and diplopia on left lateral gaze. Examination showed limitation of left eye adduction and left-sided ptosis with fatigability that improved after 2 minutes of ice pack application. The remainder of her neurological examination was normal. She commenced oral corticosteroids (titrated up gradually to 1mg/kg daily) with good response. During recovery, her ptosis alternated between eyes. Her symptoms completely resolved following 6 weeks of corticosteroid therapy.

Screening thyroid function tests (TFTs), taken after her diagnosis of OMG, demonstrated biochemical hyperthyroidism with suppressed thyroid-stimulating hormone (TSH) <0.004mIU/L (NR 0.4-4) and mildly elevated free T4 of 26.9 pmol/L (NR 10-20). She had no symptoms of hyperthyroidism. An endocrinology review was arranged. On examination, she was flushed with warm, sweaty peripheries and brisk reflexes. There was no evidence of goitre, thyroid thrill or bruit, and no proptosis or eyelid retraction.

Further testing revealed a significantly elevated thyrotropin receptor antibody (TRAb) of 14.2 IU/L (NR < 2.1), positive anti-thyroglobulin of 20.1 IU/mL (NR <4.1) and negative anti-thyroid peroxidase. She was diagnosed with Graves' disease and commenced on Neo-Mercazole (carbimazole). Thyroid ultrasound showed increased

vascularity, a non-specific finding commonly seen in Graves' disease, and no thyroid nodules. Coeliac serology, anti-GAD, anti-IA2 and anti-insulin antibodies were all negative; and morning cortisol, adrenocorticotrophic hormone and parathyroid hormone were normal.

She tolerated all medications well. Thyroid function tests normalised with biochemical euthyroidism after 5 months and TRAb returned to the normal range after 1 year. Steroids were slowly weaned and she remained symptom-free. The pyridostigmine was also weaned without complication. At 2 years since diagnosis, symptoms have not recurred nor progressed to generalised MG.

Discussion

There is a well-known association in adults between autoimmune thyroid disease (including Graves' disease) and MG, particularly OMG (1,3-5). There have only been a small number of reported cases in children, including a 10-year-old boy and a 7-year-old girl (1,2). This case of a 5-year-old is the youngest case we have found in the literature to date.

Juvenile myasthenia gravis (JMG) is an autoimmune disorder featuring fatigable skeletal muscle weakness caused by the development of autoantibodies against the AChR or related molecules, with decreased AChR activity and subsequent disruption of neuromuscular junction function (6,7). OMG refers to cases with isolated ocular muscle involvement (extraocular muscles, levator palpebrae and orbicularis oculi) and no progression to generalised myasthenia within 2 years. (6-9).

OMG may present with ptosis, strabismus or diplopia, and is more common in children than adults (6,10,11). Children with OMG have lower rates of AChR antibody positivity (41-54%) than those with generalised JMG, (72-82%) (6,7,10). OMG may progress to generalised JMG, however this is less common in children, with rates of progression ranging from 8-33% in children (6,10,12) compared to 50-70% in adults (10,12). Childhood-onset OMG has a higher rate of disease resolution than in adults; even without complete resolution, most children respond to medical management with first-line agent pyridostigmine or in combination with corticosteroids (8,10,12).

Clinical presentation of MG varies between populations. Higher rates of isolated OMG occur in children of Asian descent (up to 71-93% of East Asian children (10,11)) and paediatric onset of MG is also more common in East Asian populations (11,13). Zhang et al reported onset of MG before age 15 in 50% of 391 patients from mainland China, with a majority (75%) of these childhood cases being isolated OMG (11). This compares to paediatric cases representing 10-15% of MG in Caucasian

and African-American populations (8). Correlations exist between several human leukocyte antigen (HLA) genes and MG, suggesting genetic susceptibility (11,14,15). In East Asian populations, the HLA-DRB1*09 allele (which is rare in Caucasians) has demonstrated association with MG, in particular early-onset disease and OMG (14,15). Other implicated genes include HLA-B*08 and HLA-DR3 (3,4,15). Antibody positivity rates also vary between populations, with high reported rates of AChR antibody positivity (>60%) in mainland China (11).

Graves' disease, the commonest cause of hyperthyroidism in children (incidence 1-14/100,000), is an autoimmune disorder in which TRAbs cause thyroid gland stimulation and excess thyroid hormone secretion (16-18). Graves' ophthalmopathy can occur due to cross-reactivity of TRAbs with a TSH receptor-like protein in extraocular muscles and retroorbital tissue, leading to inflammation of intraorbital contents with periorbital oedema, proptosis, eyelid retraction and impaired extraocular muscle movements (18,19). While extraocular muscle movements can be affected in both diseases, proptosis and lid retraction differ from the ptosis and fatiguability seen in MG (6,7). Graves' ophthalmopathy is less common and generally less severe in children than adults (18,19).

Graves' disease occurs in 6% of patients with MG (4) (vs. 0.5% of males and 3% of females in the general population (20)) but there are few reports of this co-existence in children (1,2). The underlying pathogenesis is not fully understood. HLA-DQ3 and HLA-DR3 have been suggested to convey genetic susceptibility to the co-existent disorders, and antibody positivity and response to steroid treatment support autoimmune pathogenesis (3,21). Those affected by MG with associated autoimmune thyroid disease may have a milder clinical course than those without thyroid involvement, characterised by isolated ocular involvement with less frequent generalisation, lower frequency of thymus involvement and lower AChR antibody positivity (3,8).

Childhood-onset OMG typically responds well to treatment and is less likely to progress to generalised disease than in adults (8,10,12,22). Treatment of OMG co-existent with Graves' disease is less predictable and approaches vary. Several authors report improvement of MG symptoms with lowering of thyroid hormones; the child in our case commenced carbimazole despite only a mildly elevated T4 because of literature suggesting aggressive treatment may improve the ocular prognosis (21,23). However, others report a "see-saw" phenomenon of worsening of myasthenic symptoms with treatment of thyrotoxicosis (24). Ratnakorn and Vejjajiva (5) found high-dose prednisolone successfully induced remission in hyperthyroidism and MG, in adults,

without the need for anti-thyroid drugs, however, there are no reports of this approach in children. In our case there was an initial improvement with pyridostigmine, however, symptoms progressed and prednisolone was commenced about one week prior to the introduction of carbimazole to treat hyperthyroidism. This led to rapid resolution of symptoms. Following symptom resolution, steroids were weaned successfully without rebound worsening of thyroid disease. The role of thymectomy is well established in adult patients and results in lower MG relapse rates in those with MG and hyperthyroidism (5). Thymectomy is not routinely indicated in pre-pubertal children with OMG and was not considered in this case but could be considered in refractory cases (13,25).

In conclusion, we report the case of a 5-year-old girl with OMG and Graves' disease who experienced incomplete response to pyridostigmine, with remission induced following the introduction of prednisolone and treatment with carbimazole. Even in young children, this association should be investigated. Early introduction of steroids should be considered in affected children, to induce remission, treat associated thyroid disease and prevent potential see-saw phenomenon with antithyroid medications.

Acknowledgements

Dr. Manoj Menenzes for performing electromyography.

Corresponding Author

Olivia Watson

olivia.watson@health.nsw.gov.au

Sydney Children's Hospital Randwick, High St

Randwick NSW Australia 2031,

phone: +61 2 93821111.

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