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Complete remission induced by rituximab in refractory, seronegative, muscle-specific, kinase-positive myasthenia gravis

Rituximab is a chimeric IgG1 κ monoclonal antibody that targets CD20, a transmembrane phosphoprotein on most B cells. Rituximab depletes B cells by binding to the CD20 molecule and initiating complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity.¹

Recently, there was a case of muscle-specific kinase (MuSK)-positive myasthenia gravis (MG) successfully treated with rituximab.²

We report a patient with MuSK-positive generalised MG who achieved complete remission with rituximab, after being refractory to steroids, intravenous immunoglobulin, immunosuppressants, thymectomy and less responsive to plasmapheresis.

A 32-year-old man was referred for refractory MG. He gave a 2.5-year history of mild bulbar and generalised weakness, mostly in proximal extremities, without sensory symptoms. He denied ptosis and diplopia but reported mild dysphagia and dysarthria. Family history was negative for neuromuscular disorders. He was receiving no medications. He denied any history of smoking and drank socially.

The general physical examination was unremarkable. Neurological examination demonstrated diplopia on extreme lateral gaze without fatigable ptosis or Cogan's lid twitch sign. There was moderate weakness of facial muscles bilaterally and of the tongue, without atrophy. He had mild dysarthria without voice fatigue and mild proximal limb weakness with sustained shoulder abduction for 10 s. No neck weakness was detected. He could perform 10 squats without difficulty. Sensation, gait, coordination and deep tendon reflexes were

all normal except for mild hyporeflexia at the ankles. Plantar responses were flexor.

Initial investigations elsewhere included baseline 2 Hz repetitive nerve stimulation with decremental responses of 17% at the right median and 66% at the right musculocutaneous nerves without post-exercise facilitation, a negative Tensilon test with simultaneous measurement of forearm and grip strength, and repetitive nerve stimulation of the median nerve 2 h before and 2 days after 120 mg of Mestinon, and a negative acetylcholine-receptor antibody panel. A muscle biopsy did not show any myopathic features.

His symptoms had not responded to a 1-month trial of pyridostigmine at maximal doses of 240 mg/day. Prednisone at 60–80 mg/day for 2 years had been ineffective. A thymectomy had been performed 2 years before, which revealed thymic hyperplasia, but he had failed to improve. Azathioprine caused hepatotoxicity with jaundice. His condition deteriorated and he developed profound, mainly proximal upper and lower limb weakness. The only beneficial treatment was plasmapheresis, and he eventually obtained good control with three exchanges per week, alternating with two exchanges per week. Plasmapheresis was suspended briefly to try intravenous immunoglobulin 2 g/kg, but his condition worsened dramatically, and plasmapheresis was re-started.

Ciclosporin (150–200 mg twice daily) was added to stabilise his condition and to reduce his dependence on plasmapheresis, with some success. At times he had no limb weakness, but the moderate to severe facial and tongue weakness did not change. After 5 years, his condition began to deteriorate slowly, becoming less responsive to plasmapheresis, and he became continuously weak. Mycophenolate mofetil (1000 mg twice daily) was added for 3 months, but without success. A 6-month trial of cyclophosphamide IV, 1 g/m² surface area every month, also provided no benefit.

When the assay became commercially available, MuSK antibodies were found; titres were not measured. A repeat CT showed no residual thymic tissue. His condition continued to decline despite plasmapheresis three times a week, and so treatment with rituximab was started 3 months after his last dose of cyclophosphamide. He received four doses of rituximab 375 mg/m² every week for two cycles and noted improvement of his symptoms after the first cycle. After that, he received one infusion every 10 weeks. After several months, he was able to discontinue plasmapheresis, and has remained off all other medications for 1.5 years. Rituximab infusions were stopped 6 months ago after 1 year of treatment and he remains in complete remission. MuSK antibodies have not been checked for again because of insurance restrictions.

A chimeric murine/human IgG1 κ monoclonal antibody against CD20, rituximab depletes B cells by binding to the CD20 molecule and initiating complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity,¹ hence providing therapeutic benefit for many B cell-mediated diseases. Rituximab is a Food and Drug Administration-approved drug for the treatment of relapsing/refractory CD20-positive low-grade non-Hodgkin's lymphoma. Rituximab has been used successfully with other autoimmune neuromuscular diseases. Side effects include severe or fatal infusion reactions, infections, hypersensitivity, cardiac

arrhythmias, renal toxicity, bowel obstruction and perforation.

Previous reports have described refractory generalised seropositive MG responding serendipitously to rituximab when MG arose in association with bone marrow transplantation or with lymphoma.^{3–5} Recently, there was a report of a 56-year-old woman with bulbar MuSK-positive MG refractory to prednisone, azathioprine and mycophenolate mofetil, but less responsive to plasmapheresis, who had improved with 2 months of rituximab treatment. She has been stable for 12 months, but needed to be re-treated with Mestinon and mycophenolate mofetil 1000 mg/day, 3 months after the first rituximab course.² Ours is the second case of isolated refractory seronegative, MuSK-positive MG achieving complete remission after receiving rituximab, and the first case to achieve and maintain this for over 1.5 years. Rituximab provides more selectivity in targeting B cells compared with immunosuppressants such as ciclosporin, azathioprine and mycophenolate mofetil, which makes this an attractive treatment choice for MG. Rituximab should be considered as a treatment option in MuSK-positive MG refractory to other immunomodulatory agents.

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Aggravation of ataxia due to acetazolamide induced hyperammonaemia in episodic ataxia

Acetazolamide has been used to reduce the number of attacks in patients with episodic ataxia type 2 (EA 2), presumably by inhibiting

carbonic anhydrase, which results in brain acidosis and reduction of brain lactate and pyruvate levels.¹ However, metabolic acidosis itself may give rise to several clinical manifestations, and there have been case reports describing drowsy mentality with metabolic acidosis by acetazolamide intoxication.^{2,3} We report on a patient with EA 2, who initially had a good response to acetazolamide for 2 years but later developed aggravation of ataxia with drowsy mentality caused by acetazolamide induced hyperammonaemia.

Case report

A 49-year-old man reported dizziness and ataxia which had started 4 days before admission. He had experienced several episodes of similar symptoms for the past 4 years. He had recurrent episodes of headaches, dizziness, nausea/vomiting, dysarthria and ataxia which had lasted for hours to days. Between the episodes, he showed gaze evoked nystagmus without spontaneous nystagmus. Horizontal head thrust tests were normal. Vibratory stimuli on both mastoids, horizontal head oscillation or hyperventilation did not induce nystagmus. Other findings of the neurological examination were normal. During the episodes, examination disclosed downbeat and aggravated gaze evoked nystagmus, rebound nystagmus, positional downbeat nystagmus, impaired smooth pursuit, hypometric saccades, slurred speech, and gait and limb ataxia. Vibratory stimuli on both mastoids, and horizontal head oscillation augmented downbeat nystagmus. Routine blood chemistry, EEG, CSF studies and brain MRI were normal. Genetic studies were unavailable. He denied any other diseases, including hypertension, diabetes, and liver or kidney disease. He did not have a history of seizure or inborn errors of metabolism, and did not take any medication or alcohol. He denied a family history of ataxia or other diseases. Based on the above findings, he was given acetazolamide 250 mg four times a day with a presumptive diagnosis of EA 2 from 2 years previously. The patient reported that the frequency and severity of attacks were significantly decreased after taking acetazolamide for 2 years.

With this attack he was found to have gaze evoked nystagmus, positional nystagmus, dysarthria and aggravated gait ataxia, which was similar to the previous attacks. This time, however, he was drowsy and was unable to speak unless painful stimuli were given. The Glasgow Coma Scale was measured as E3V4M6. His vital signs were normal. He was not taking any other medication except for acetazolamide 250 mg four times a day. He had suffered a mild upper respiratory tract infection 1 week prior to the event.

In view of the decreased mentality, routine blood chemistry, urinalysis, CSF studies and brain MRI were performed to exclude any other causes that might explain his decreased mentality. Again his brain MRI was normal, without any lesion or atrophy involving the cerebellum or brainstem. Laboratory data showed hyperammonaemia at 158 µg/dl (normal 8–48) and metabolic acidosis compensated by respiration with a pH of 7.39 (normal 7.38–7.46), pCO₂ of 23.4 mm Hg (normal 32–46) and HCO₃⁻ of 13.9 mmol/dl (normal 21–29). Other findings on blood chemistry, urinalysis and CSF studies were normal. Amino acid analysis in the serum and urine, and abdominal CT, which were performed to exclude

underlying liver disease or enzyme defects, showed no abnormality. He was maintained on acetazolamide but 3 days later ammonia levels increased to 660 µg/dl while ataxia and dysarthria were severely aggravated. After discontinuation of acetazolamide, his symptoms began to improve, and 10 days later serum ammonia had decreased to 122 µg/dl when his symptoms almost resolved. He was considered to suffer from acetazolamide induced hyperammonaemia and discharged without acetazolamide medication.

Comment

This is the first case showing an attack of ataxia due to acetazolamide induced hyperammonaemia in a patient with clinically diagnosed EA 2. Even though our patient denied a family history of ataxia and rejected genetic studies, the clinical manifestations and initial good response to acetazolamide suggest EA 2 as the most probable diagnosis. However, during the last episode, our patient had also developed a reduced level of consciousness, a rare manifestation of EA 2, which prompted us to search for causes other than EA 2. Laboratory data were normal except for hyperammonaemia which decreased markedly after discontinuation of acetazolamide, along with resolution of his symptoms. The level of arterial ammonia was proportional to the severity of his symptoms, and hyperammonaemia was normalised by discontinuing acetazolamide, without any further aggressive management such as haemodialysis. A recent history of upper respiratory tract infection might have influenced drug metabolism and caused hyperammonaemia but we failed to find any distinct cause explaining the acute adverse effect of acetazolamide.

The kidneys contribute to the acid-base balance by reabsorbing filtered HCO₃⁻ and excreting H⁺ in the form of titrate acid or ammonium. The ability to excrete H⁺ as ammonium contributes to the flexibility of the renal acid-base regulation as the rate of NH₄⁺ production and excretion can be modulated according to physiological needs. Acetazolamide, a carbonic anhydrase inhibitor that mainly acts on the proximal tubule of the kidney, induces metabolic acidosis by inhibiting bicarbonate reuptake. In metabolic acidosis, the kidneys increase NH₄⁺ excretion in two ways: by increasing proximal NH₄⁺ production from glutamine and by lowering urine pH, which would increase NH₃ diffusion into the lumen and result in NH₄⁺ production in combination with H⁺.⁴ The increased production of NH₃, caused by metabolic acidosis, and the relative decrease in H⁺ in the tubular lumen due to a carbonic anhydrase inhibitor, such as acetazolamide, give rise to hyperammonaemia, as in our patient.

Hyperammonaemia is an important cause of acute metabolic encephalopathy and a potentially lethal condition, and a differential diagnosis of hyperammonaemia must include liver disease, renal disease, critical medical conditions such as hypovolaemia or sepsis, and drug induced and enzyme defects (eg, urea cycle and organic acid disorders). Prompt management must be taken, which includes hydration with adequate urine output, removal of nitrogen by dialysis or medication, discontinuation of protein intake and minimisation of catabolism.

Acetazolamide was initially introduced as a diuretic but is now widely used in patients

with glaucoma, epilepsy, periodic paralysis and EA. Acetazolamide should be used with caution in patients with a previous history of hepatic or renal diseases. When a patient with EA 2 shows aggravation of ataxia with reduced alertness, emergent screening of arterial blood gas and serum ammonia is warranted to exclude acetazolamide induced hyperammonaemia even after an initial good response to acetazolamide. The potassium channel blocking agent, 4-aminopyridine, could be considered as an alternative medication.⁵

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Intralabyrinthine schwannoma affecting the low but not high frequency function of the vestibulo-ocular reflex: implications for the clinical diagnosis of chronic peripheral vestibular deficits

Peripheral vestibular hypofunction can be identified by asymmetric vestibular responses to caloric irrigation of the horizontal semicircular canal or by the head impulse test.¹ Whereas the first test investigates the low frequency function of the vestibulo-ocular reflex (VOR) the latter assesses the high frequency function. The high frequency VOR function is usually more persistently impaired in unilateral vestibular lesions (eg, vestibular neuritis) than the low frequency function and thus the more sensitive parameter to detect chronic peripheral vestibular deficits.²

Contrary to this current vestibular knowledge, we present a patient with a chronic