Antibiotic neuromuscular junction myasthenic mimetics

Maartje G Huijbers and colleagues[1] are to be commended for their instructive and comprehensive Review of autoimmune neuromuscular junction disease. However, they do not discuss antibiotics that mimic some of the mechanisms of autoimmune neuromuscular junction disease and can therefore exacerbate the clinical features of neuromuscular myasthenic syndromes. International consensus guidance on the management of myasthenia gravis[2] advises against the use of aminoglycosides, macrolides, and fluoroquinolones in people with myasthenia gravis and advocates for raising awareness of the potentially serious adverse reactions of these antibiotics in patients with this autoimmune neuromuscular myasthenic syndrome. However, there is little guidance on antibiotic contraindications in Lambert-Eaton myasthenic syndrome. Aminoglycoside-mediated blockade of voltage-gated calcium channels essentially mimics the pathological mechanism of Lambert-Eaton myasthenic syndrome. Hence, aminoglycosides should, at least theoretically, be avoided in patients with this condition.

The aminoglycoside gentamicin is routinely used in common operations, such as joint arthroplasty or any trauma surgery when metalware is implanted.[3] For lower limb arthroplasty, in particular for total hip and knee replacements, gentamicin-loaded bone cement is used to fix a prosthesis to the bone. This cement elutes gentamicin into the surrounding tissues and systemic circulation. There is no explicit guidance on the use of antibiotic-laden prosthetics in people with myasthenia gravis or Lambert-Eaton myasthenic syndrome. However, bone cement manufacturers do advise caution when using their products in patients with various neuromuscular conditions, with myasthenia gravis specifically mentioned.[4] Patients with myasthenia gravis could account for up to 0·1% of all patients undergoing knee or hip arthroplasty.[5] Given that more than 1·5 million arthroplasty procedures are done annually in the USA,[5] the number of patients in whom there is potential for exacerbation of clinical symptoms is not negligible.

β blockers are another drug class that is strongly linked to exacerbation of myasthenic symptoms.[2] Because of the range of drug classes associated with exacerbation of clinical features of autoimmune neuromuscular myasthenic syndromes, antibiotic and drug interactions with myasthenia gravis and Lambert-Eaton myasthenic syndrome are relevant and can be important considerations at the time of medical and surgical treatment of patients with autoimmune myasthenic syndromes.

We declare no competing interests.

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Authors' reply

Chika E Uzoigwe and Frederick Campbell-Jones[1] highlight an important issue in medical practice for managing patients with neuromuscular autoimmune disease, and their remarks are a useful addition to our Review in the Series. Indeed, the use of particular antibiotics, muscle relaxants, and other drugs are known to worsen the disease in patients with myasthenia gravis or Lambert-Eaton myasthenic syndrome. Uzoigwe and Campbell-Jones mention gentamycin-loaded bone cement as a possible under-recognised source among these aggravating drugs.

Many drugs are associated with worsening of signs and symptoms in patients with myasthenia gravis or Lambert-Eaton myasthenic syndrome. However, reported associations do not necessarily mean these drugs should never be prescribed for patients with these conditions. Reports of disease worsening are often rare or might represent a coincidental association. Clinical judgment and the cost-benefit ratio of a drug should be considered when that drug is deemed important for the treatment of a patient with myasthenia gravis or Lambert-Eaton myasthenic syndrome.[2]

See appendix for declarations of interest.

Maartje G Huijbers, Anna Punga, Jan J Verschuuren

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Exercise training and neuroprotection in multiple sclerosis

We read with interest the Correspondence by Brian M Sandroff and colleagues[1] on exercise training in multiple sclerosis, but believe that the rationale behind this

See **Online** for appendix

This online publication has been corrected. The corrected version first appeared at thelancet.com/neurology on Aug 10, 2022

letter could have been based on misconceptions. The authors state that two systematic reviews[2,3] from our research group conclude that exercise training is not associated with neuroprotection. To clarify, the first systematic review[2] explicitly states that the evidence on the effects of physical exercise on brain volume in neurodegenerative populations appears sparse and inconclusive, most likely due to the absence of large, long-term (≥1 year), and well-designed studies. Moreover, the arguments put forward by Sandroff and colleagues[1] are the same as those outlined in the discussion of our first systematic review.[2] Hence, in the first review, according to the purpose of systematic reviews, we accurately described the existing literature and summarised the evidence leading to a balanced discussion that can help guide the direction and quality of future studies.

As for our second systematic review,[3] Sandroff and colleagues[1] appear to have overlooked its aim to summarise the existing evidence on the effects of exercise training on neurotrophic factors. Although we did note increased chronic levels of BDNF in patients with multiple sclerosis, this increase did not translate into neuroprotection in the few studies examining these levels.

Additionally, Sandroff and colleagues[1] imply that a randomised controlled trial from our group[4] did not involve a priori determined brain regions of interest for studying exercise-induced neuroprotection and relied on structural neuroimaging for generating conclusions on neuroprotection. To clarify, predefined regions of interest were registered at ClinicalTrials.gov (NCT02661555) and we applied extensive state-of-the-art diffusion kurtosis imaging in addition to volumetric neuroimaging.

We fully agree with Sandroff and colleagues[1] that a shift in scientific paradigm is slow and arduous, and that large randomised controlled trials are needed assessing the effect of exercise on neuroprotection in people with multiple sclerosis. We emphasised and thoroughly outlined this scientific paradigm shift in our 2019 review.[5]

As should be clear from our publications, we are strong advocates for exercise and its potential for eliciting neuroplasticity and neuroprotection in people with multiple sclerosis, yet we insist on balanced, evidence-based conclusions and recommendations. We encourage and welcome other research groups to help unravel the potential of exercise in multiple sclerosis, as we believe that a joint collaborative research approach is crucial.

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Interferon receptor dysfunction in a child with malignant atrophic papulosis and CNS involvement

Malignant atrophic papulosis is a rare, thrombo-obliterative vasculopathy, with either a cutaneous benign presentation or a systemic severe presentation, predominantly affecting the gastrointestinal tract, lungs, and CNS.[1] We report a heterozygous de-novo variant in the interferon α/β receptor subunit 1 gene (*IFNAR1*, MIM_107450) in a girl with malignant atrophic papulosis and CNS involvement who presented to our clinic in August, 2019, at age 9 years. Interferon signalling is dysregulated in our patient, and treatment with the Janus kinase 1/2 inhibitor baricitinib, and with anifrolumab (an antibody that blocks interferon signalling), has led to stabilisation of her signs and symptoms.

The patient is the only child of non-consanguineous, healthy, White, European parents. Pregnancy, delivery, and early childhood were uneventful. She had periodic holocephalic headaches at age 5 years. Bilateral glaucoma and signs of optic nerve atrophy were first diagnosed at age 6·5 years at another institution, requiring five surgical interventions (four trabeculectomies with mitomycin and a scleral patch), which took place within 1 year of the diagnosis, but did not stop the progression of glaucoma.

At age 7 years, the patient had multiple round, white skin lesions, 1–2 mm in diameter and with telangiectatic rims, disseminated on her entire integument. A skin biopsy showed a superficial perivascular dermatitis with traits of vasculopathy, but without signs of vasculitis (figure 1).

Acoustic evoked potentials were pathological at age 7·5 years; however, hearing loss in the right ear was not noticed until about 1 year later.