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REVIEW ARTICLE

ALSUntangled #66: antimycobacterial antibiotics.

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Abstract

Several infections have been associated with motor neuron diseases resembling ALS, including species of viruses, bacteria, and parasites. *Mycobacterium avium* subspecies *paratuberculosis* (MAP), most known for its probable etiologic association with Crohn's disease, has been suggested as another possible infectious cause of motor neuron disease. Two published case reports describe the successful treatment of ALS-like symptoms with antimycobacterial antibiotics. Both cases had atypical features. Based on these, we believe it would be reasonable to begin performing chest imaging in PALS who have features of their history or exam that are atypical for ALS such as pain, fevers, or eye movement abnormalities. If the chest imaging is abnormal, more specific testing for mycobacteria may be indicated. Until there is more clear evidence of an association between mycobacteria and ALS, we cannot endorse the widespread use of potentially toxic antimycobacterial antibiotics for PALS.

Keywords: *Amyotrophic lateral sclerosis, antimycobacterial antibiotic therapy, infectious ALS, motor neurone disease, paratuberculosis*

Overview

Species of viruses (1–5), Cyanobacteria (6,7), Mycoplasma (8), Mycobacteria (9,10), Brucella (11), and Schistosoma (12) have all been associated with motor neuron diseases resembling ALS. The theory that *Mycobacterium avium* subspecies *paratuberculosis* (MAP) might cause or trigger ALS was first mentioned in a paper published in 2015 (13) and then described in detail in a paper published in 2018 (14,15). This bacterium is most known for its probable disease-causing-association with Crohn's disease (16,17). Here, on behalf of people with ALS (PALS) who asked about this (18), we review the evidence for mycobacteria in causing an ALS-like illness and the potential of antimycobacterial antibiotics as ALS treatments.

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ALSUntangled reviews alternative and off-label treatments on behalf of people with ALS (PALS). Here, we review antimycobacterial antibiotics.

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Mechanistic plausibility

Apoptosis (a specific form of programmed cell death) rather than necrosis is considered to be the type of motor neuron death in ALS (19). Bacteria can cause neuronal apoptosis via caspase activation and reactive oxygen species (20). A study published in 2004 demonstrated that intracellular MAP organisms can secrete a variant zinc/copper superoxide dismutase that contains copper but completely lacks zinc (21). Zinc-deficient copper containing superoxide dismutases are thought to cause neuronal apoptosis by two possible mechanisms: (1) the induction of nitric oxide production (22), which then causes neuronal apoptosis by oxidant activation of either the p53/p38 MAPK pathway or endoplasmic reticulum stress (23), or (2) the enhanced catalysis of tyrosine nitration by peroxynitrite (24). Given these theoretical mechanisms we assign a Table of Evidence (TOE) grade of D (Table 1). Oddly, some data suggest that MAP has antiapoptotic effects in infected bovine, ovine, and human macrophages (25,26).

Pre-clinical models

There are no studies of antimycobacterial antibiotics in classic pre-clinical animal models of ALS. We therefore assign a "pre-clinical" TOE grade of U (Table 1). Of interest, injection of *Mycobacterium avium* organisms into the foot pads of mice can cause degeneration of their sciatic nerves (27). This somewhat supports the theory that transcutaneous MAP exposure could lead to motor neuron loss in humans (14).

Patient case reports

We found 2 case reports of ALS-like illnesses responding to antimycobacterial antibiotic therapy (9,10). Details of these can be found in the Supplemental Data. Both cases had upper and lower motor neuron signs, but because of atypical features such as eye movement abnormalities, extremity pain, cough, and low grade fevers, chest imaging was performed which eventually led to the diagnosis of and treatment for *Mycobacterium tuberculosis* (MTB). Based on these published case reports, both of whom had some atypical features for an ALS diagnosis, we assign a TOE "cases" grade of A (Table 1).

Dosing, risks, and costs

Optimal antibiotic dosing for mycobacterial infection in association with motor neuron disease has not been established. The first case report (9) did not describe the particular antibiotics used in the patient's "anti-tuberculous treatment." The second case report (10) used two months of isoniazid (225 mg/day total), rifampicin (450mg/day total), ethambutol (825 mg/day total), and pyrazinamide (1200 mg/day total), followed by four additional months of the above regimen minus the pyrazinamide. Details on mycobacterial treatments in other conditions (28–56) can be found in the Supplemental Data.

Rifabutin can cause leukopenia, neutropenia, thrombocytopenia, and hepatitis requiring laboratory monitoring (57). Rifabutin at the high dose of 600 mg/day, especially in combination with a macrolide antibiotic such as clarithromycin, can result in reversible anterior uveitis in a significant proportion of patients depending on their immune status (58,59). The treatment of drug-induced uveitis "occasionally" involves hospitalization (60). Clarithromycin can cause a metallic taste, 10% of patients may have nausea, diarrhea, abdominal pain, and/or headache (61), and there is an increased rate of sudden cardiac death compared to other antibiotics of 37/million clarithromycin doses (62). Clofazimine almost always causes brownish skin discoloration, and sometimes abdominal pain, but these side effects led to discontinuation of treatment in only 0.1% of patients (63). Nausea, vomiting, diarrhea, and abdominal pain are common side effects of metronidazole (64). Encephalopathy (65) and optic neuropathy (66) are rare side effects of metronidazole and are usually reversible with discontinuation of the drug. Based on these rare but potentially serious side effects, we assign a TOE "risks" grade of D

Table 1. Table of evidence for antimycobacterial antibiotics.

	Grade	Explanation
Mechanism	D	MAP can theoretically cause motor neuron death via apoptosis by secreting zinc absent copper containing SOD; oddly some data suggest that MAP can also be anti-apoptotic.
Pre-Clinical	U	We found no studies of anti-MAP therapy in ALS models.
Cases	A	Two case studies of patients with MTB and atypical ALS symptoms had the latter improve with antimycobacterial antibiotics.
Trials	U	We found no clinical trials of antimycobacterial antibiotics in PALS.
Risks	D	Rare antibiotic-associated encephalopathy (metronidazole). Rare sudden cardiac death (clarithromycin). Rare optic neuropathy (metronidazole). Frequent uveitis (rifabutin) in immunocompromised patients occasionally requiring hospitalization.

(Table 1). Of additional interest, one case-control study suggests that any antibiotic use might increase the risk of developing ALS as well (67).

The cash price of rifabutin (68) in the U.S. is approximately 1200 US dollars for 100 150 mg capsules or 1440 dollars per month for four capsules (600 mg) per day. The cash price of clarithromycin (69) is approximately 30 US dollars for twenty 500 mg tablets or 90 dollars per month for two tablets (1000 mg) per day. Although the World Health Organization classifies clofazimine as an essential medicine (70), it is only available in the United States as an investigational new drug via Novartis' Managed Access Program (71). It is provided to patients under this program at no cost. The cash price for metronidazole (72) is approximately ten dollars per 500 mg tablet, or 600 US dollars per month for two tablets (1000 mg) per day.

Conclusion

There is a theorized association between MAP and ALS, and two published case reports described improvements in ALS-like conditions (both with atypical features) after treatment with antimycobacterial antibiotics. Based on these, we believe it would be reasonable to perform chest imaging in PALS who have features of their history or exam that are atypical for ALS such as pain, fevers, or eye movement abnormalities. If the chest imaging is abnormal, more specific testing for mycobacteria may be indicated. Until there is more clear evidence of an association between MAP and ALS, we cannot endorse the widespread use of potentially toxic antimycobacterial antibiotics for PALS.

Declaration of interest

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