Immunosuppression & Mycotoxins Causing Amyotrophic Lateral Sclerosis

WILLIAM REID

1. Hematology & Oncology, Franklin, TN
2. Lawton Indian Hospital, Lawton, OK

Amyotrophic Lateral Sclerosis (ALS) has remained a terminal disease without a clear underlying pathogenesis for the majority of patients. It is known to cluster around heavily polluted environments. I began evaluating patients with ALS in 2003 finding they all had evidence of immunosuppression with Hypogammaglobulinemia, Lymphopenia and Anergy on skin testing. They all had evidence of a toxic exposure with elevated Protoporphyrins with adequate Iron Stores. They all had developed a Metabolic Acidosis with an elevated Anion Gap. They all had elevated Kreb Cycle Intermediates on urine screen for Organic Acids consistent with Mitochondrial Damage. Muscle biopsies were positive for only ALS. Screens for the standard poisonings, lead, arsenic, mercury were negative. Studies for the Mycotoxin, Trichothecene were positive. Given the evidence of Immunosuppression the patients were given Gammaglobulin. They were given trials of Amphotericin and Fluconazole without an apparent effect. Trials of Voraconazole routinely corrected the Protoporphyrinemia and the Anion Gap Metabolic Acidosis. In addition, the Krebs Cycle Intermediates returned to normal. On stopping Voraconazole, the findings recurred. There was no apparent improvement in the patients neurologic deficits. The patients were given Plasma Exchange as a 5 day procedure similar to the procedure for Guillain-Barre along with Voraconazole. Again the Protoporphyrimenia and Anion Gap Metabolic Acidosis resolved. In addition, the patients began to show reversal of their neurologic deficits confirmed with Maximum Pressure Inspiratory measurements. In one patient paralyzed from the waist down for over a year, he began walking documented in the hospital. In another patient with Bulbar ALS his pulmonary function returned to normal on the fifth day of plasma exchange.

In 1993 I reported to the Tennessee Department of Health that there was a cluster of patients with amyotrophic lateral sclerosis (ALS) living around and working at the nuclear weapons facility in Oak Ridge, TN. This was confirmed by representatives of the Tennessee Department of Health. 1

More than 10 years later, I began managing the care of a patient with terminal ALS paralyzed from the neck down and ventilator dependent. She was immunosuppressed as evidenced by having hypogammaglobulinemia, lymphopenia, anergy to skin testing to Candida and Trichophyton and with yeast cultured routinely from urine and a tracheostomy. Her labs showed persistently elevated protoporphyrins without iron deficiency. She had persistently low CO2 consistent with a metabolic acidosis with elevated anion gap. A urine screen for organic acids found multiple elevated Kreb cycle intermediates consistent with a mitochondrial injury. Analysis of a muscle biopsy was consistent with only ALS. Due to the secondary porphyria, tests for a toxin were done, but were uniformly negative including lead, arsenic,
unrestricted use, distribution, and redistribution in any medium, provided that the original author and source are credited.

Mercury and other metals. Given the findings of immunosuppression she was given gammaglobulin and an infectious etiology was considered to explain the porphyrins and metabolic acidosis. Trials of anti-fungal agents including Amphotericin and Fluconazole were without effect. However, Voraconazole treatment resulted in normalization of the patient's porphyrins and metabolic acidosis. There was no evidence of any clinical improvement with respect to the paralysis. A trial of plasma exchange was done following a protocol similar to that for Guillain-Barre with 5 days of 1.5 liters/day along with the Voraconazole and gammaglobulin. She began to recover functions in her right hand and again her porphyrins and metabolic acidosis resolved.

Based on the findings from this case, other ALS patients were evaluated. All had evidence of immunosuppression, involving both humeral and cellular mechanisms, as well as secondary porphyria. The extent of the paralysis paralleled the degree of immunosuppression. The patients had lymphopenia, anergy to skin testing, hypogammaglobulinemia, depressed lymphocyte mitogen stimulation to candida and depressed natural killer cell function. The pattern of porphyrins was most consistent with secondary etiology due to toxins with elevated protoporphyrins and coproporphyrins. Many had low CO2 levels and metabolic acidosis, but even without this, they had elevated organic acid levels due to Kreb cycle intermediates consistent with a mitochondrial injury. Trials of voraconazole and gammaglobulin with plasma exchange consistently corrected the porphyria and the acidosis and resulted in either stabilization or recovery of motor function.

REVIEW OF LITERATURE:

Amyotrophic lateral sclerosis/motor neuron disease is a neurodegenerative disorder causing progressive, relentless muscle weakness with eventual death with median survival of 3-5 years. The etiology has remained obscure for the majority of patients. The pathology of the disease finds selective motor neuron degeneration. Studies of signal transduction pathways in patients with ALS using immunohistochemical analysis show abnormalities in c-Jun, JNK/SAPK kinase, and evidence of oxidative stress.

Epidemiologic data have for years implicated an environmental event. There is a 2 fold increase in ALS in young US Gulf War veterans. As noted above, there is a cluster of ALS in workers from the Oak Ridge Nuclear Weapons facility. There is a high prevalence of ALS in the Western Pacific especially Guam, Western New Guinea and Kii Peninsula of Japan. Studies at UCLA were done of tissue cultures with murine anterior horn cells. Serum from patients with 17 different neurologic disorders had no negative effects on the cultures, but in the cultures using serum from ALS patients in 70% there was accelerated death of the anterior horn cells. Based on the epidemiology and lab studies, ALS patients were treated with plasma exchange with uniformly negative results.

Immunodeficiency was documented in all the patients involving both cellular and humeral immunity. The same environmental exposures reported in clusters of ALS could also be responsible for immunodeficiency. Radiation causes a profound lymphopenia and can cause immune deficits at subclinical levels. Natural killer cell function deficiency can be due to corticosteroids, alcohol, salicylates, theophylline as well as environmental toxin predisposing to herpes infections. The patients had anergy on skin testing to candida and trichophytin as well as had depressed lymphocyte mitogen stimulation to candida predisposing to mycobacteria and fungi. Certain opportunistic fungi such as the fusarium species have become prominent problems in immunocompromised patients.
The mycotoxins released from opportunistic infections could be responsible for the pathology found in ALS. Trichothecene is a mycotoxin from fusarium and several other species. It causes findings similar to ALS on a molecular level\(^6,20,21\) with oxidative stress and mitochondrial damage. The key moiety is the epoxide ring\(^9,22\) which targets peptidyltransferasse, an enzyme in the 60 S ribosomal subunit linking amino acids and generating ATP. This would explain the elevated Kreb cycle intermediates in the patients. In addition trichothecenes cause immunosuppression\(^21\). Fusarium is ubiquitous in the worldwide food chain\(^21,23\). Trichothecenes are lipophilic, low molecular weight toxins (MW 250-550) with the structure of a sesquiterpenoid\(^9\). The epoxide moiety is critical to the pathogenesis and if removed leaves the molecule harmless. It generates free radicals which could explain the success of free radical scavengers in ALS research. Trichothecenes rapidly form a covalent bond to proteins. They are cytotoxic to most eukaryotic cells rapidly shutting down protein synthesis. This triggers ribotoxic stress response that activates JNK1, stress-activated MAP kinase and apoptosis\(^6\).

**PATIENTS:**

Below are summarized the findings with 4 patients. Similar findings have been observed with others.

1. MP- ventilator dependent, paralyzed from the neck down, lymphopenia, hypogammaglobulinemia, elevated RBC protoporphyrin, elevated anion gap metabolic acidosis. Treatment: All the labs for the patient were corrected with treatment by Voraconazole and/or plasma exchange.

2. JY- ventilator dependent, paralyzed from neck down, porphyria, metabolic acidosis, lymphopenia, hypogammaglobulinemia. Treatment: The patient responded to Voraconazole and plasma exchange with recovery of leg function and overbreathing on the ventilator along with correction of acidosis and porphyria

3. EH- paralyzed from the waist down with intense spasticity in the legs, porphyria, metabolic acidosis, hypogammaglobulinemia, and lymphopenia. Treatment with plasma exchange and Voraconazole resulted in correction of hypogammaglobulinemia, porphyria, and acidosis and also resulted in a remarkable recovery of motor function

4. CM- early phase ALS. The patient was given mesenchymal stem cell therapy, a treatment known to cause immunosuppression, and it resulted in accentuation of the paralysis and with labs showing RBC Protoporphyrin 100, CO2 12, Anion Gap 20, natural killer cell deficiency 5 (normal >8), hypogammaglobulinemia subclass IgG2 280(normal >350) , mitogen stimulation for Candida depression. Treatment with gammaglobulin, Voraconazole and plasma exchange resulted in elevation of natural killer cells to 12 and stabilization of the paralysis.

5. JH- patient with Bulbar ALS with impending respiratory failure. He refused intubation but agreed to Plasma Exchange and Voraconazole. After 5 days of plasma exchange with Voraconazole his Maximum Inspiratory Pressure rose to normal from zero.

**HYPOTHESIS:**

Immunosuppression of both humeral and cellular mechanisms is evident in all the ALS patients studied. The severity of immunosuppression correlated with the extent of the ALS. It is hypothesized that the immunosuppression leads to infections with opportunistic microbes that leads to the release of toxins responsible for the findings in ALS with the toxin targeting the
mitochondria in skeletal muscle. The response to Voraconazole implicates a fungus such as
fusarium which releases an array of mycotoxin including trichothecene. Voraconazole
penetrates the cerebral spinal fluid (CSF) well. This could be interpreted as evidence of a focus
of infection in the CSF. The failure of plasma exchange in the past could be due to the
persistent production of toxins by an infection. The addition of gammaglobulin and Voraconazole
to plasma exchange appears to have succeeded in inducing recovery of motor function.

REFERENCES

1. Tennessee Health Department. Final report of the Oak Ridge Health Agreement


3. Brooks BR. Revised criteria for the diagnosis of amyotrophic lateral sclerosis. In:
Amyotrophic lateral sclerosis and other motor neuron disorders; 2000; 1: 293-


eds. Clinical Hematotoxicology, Clinical Environmental Health and Toxic Exposures; 2001: 378-

6. Shifrin VI, Anderson P. Trichothecene mycotoxins trigger a ribotoxic stress response that
activates c-Jun N-terminal Kinase and p38 mitogen-activated protein kinase and induces

7. Bacman SR, Bradley, W.G., Moraes CT. Mitochondrial involvement in amyotrophic

Medicine 2003;348:2657-2668.

General WRMC, ed. Textbook of Military Medicine: Medical Aspects of Chemical and Biologic

10. Zapor and Fishbain. Biologic toxins as agents of warfare and terrorism. Respiratory Care

11. Bornstein M. Tissue culture studies of structural and functional alterations of the nervous
system related to the demyelinating disorders. In: Bailey OT, Smith DE, eds. The Central
Nervous System: Some Experimental Models of Neurological Disease. Baltimore: Williams and
Wilkins Co.; 1968:71-86.


13. Wolfgram F, Myers L. Amyotrophic lateral sclerosis: effects of serum on anterior horn

14. Wolfgran F. Blind studies on the effect of amyotrophic lateral sclerosis sera on motor


19. Orange JS, Ballas ZK. Natural killer cells in human health and disease. Clinical Immunology 2005;118:1-


