

A Recipe for ALS

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Amyotrophic lateral sclerosis (ALS) is a dreadful disease associated with progressive motor neuron degeneration with an incidence of 2-3/100,000 and affecting 2500 to 3000 Canadians at any time. The disease typically progresses to death within five years after the onset of symptoms. Since its description in 1869 by Dr. Jean-Martin Charcot, physicians and scientists have been hypothesizing what causes this fatal disease. Despite years of research, we still cannot determine what triggers the majority of sporadic cases. Even in hereditary cases, which only account for 5-10% of total cases, specific mutations have not been found for the majority of affected families. Also, there is incomplete penetrance for some of the autosomal dominant gene mutations.¹ What triggers the disease in some of these family members, or what protects other family members is unknown.

There are a number of agents that may be considered possible causes of sporadic ALS. There are theories of environmental toxins, genetic predisposition, infection, inappropriate stress responses, toxic intracellular inclusions and autoimmune disease. Shaw and colleagues are investigating how environmental toxins, such as steryl glycosides, can induce motor neuron disease.² Recently, there have been several publications identifying possible normal genetic variations that may increase susceptibility for development of sporadic ALS.^{3,4} Reverse transcriptase appears to be elevated in ALS, raising the possibility of a retrovirus contributing to the development of ALS.⁵ However, a specific virus has not yet been identified. Alteration in heat shock proteins may also be associated with ALS. Arimoclomol, an inducer of heat shock proteins, has been found to delay disease progression in a mouse model of ALS,⁶ and is in a phase 2 clinical trial in humans.

Recently, the TAR binding protein 43 (TDP-43) has been shown to be associated with cytoplasmic inclusions in both frontotemporal dementia and in sporadic ALS.⁷ The protein, which may be involved in protein transcription, may be a significant player in the pathophysiology of ALS. Since its reported association with ALS in October 2006, TDP-43 has generated a substantial amount of interest in the field of ALS research. Whether the sequestered TDP-43 is prevented from performing its normal functions or whether the inclusions are independently toxic, is a matter of debate.

Intracellular inclusions causing cell injury is a mechanism shared by several other neurological disorders, including trinucleotide repeat disorders. An interesting new publication postulates that lithium may increase the clearance of these inclusions in ALS via autophagy.⁸ The authors report a significant improvement in SOD1 mice treated with lithium, and also report remarkable improvement in survival in a small human clinical trial. Other clinical trials are being planned to determine if these results are reproducible.

Whether ALS is an autoimmune disease is an intriguing question. There have been a number of reports of autoantibodies found in ALS patients. Whether these antibodies are pathogenic or are just a marker of the disease process is unclear. It is

possible that these auto-antibodies have been summoned to clean up the debris left by another process, such as a retroviral infection, an inappropriate stress response in a cell, or an exotoxin affecting a cell. Li et al (this issue)⁹ have attempted to evaluate whether ALS IgG from human serum affects motor neurons in culture. They collected and purified IgG from six ALS patients and then applied the IgG to organotypic spinal cord cultures which preserve the horizontal architecture of the spinal cord. There was no apparent effect of the ALS IgG on motor neuron survival in organotypic cultures as compared to control IgG.

This negative study does not help us make any conclusions regarding autoimmunity in ALS. It is possible that since ALS is a heterogeneous disorder, the six ALS patients who donated their serum may not have had autoimmunity as a significant etiological factor. Pagani et al have suggested that approximately 50% of ALS patients have autoantibodies to nerve terminals.¹⁰ Therefore, it is possible that by chance alone none of the patients included by Li et al had significant autoantibodies. Despite not giving us conclusive evidence regarding the role of autoimmunity in ALS, the authors have demonstrated a useful tissue culture technique that will be useful in evaluating motor neuron survival in their native environment. As there is clear evidence that microglia and astrocytes play a role in the pathophysiology of ALS,¹¹ evaluating motor neuron survival in an environment that mimicks physiological conditions appears to be of great importance.

It is possible that we will be able to use the immune system in our favour to treat ALS. Rakhit et al have created an antibody to misfolded SOD1 protein.¹² Misfolded SOD1 proteins are of particular importance in autosomal dominant cases where the misfolded mutant protein is toxic to the cells. However, there is some evidence that oxidized wildtype SOD1 protein can cause SOD1 misfolding.¹³ If this toxic misfolded protein can be cleared from the body via an immune mediated mechanism, then we could potentially prevent the disease from progressing in both sporadic and hereditary cases of the disease.

The pathogenesis of sporadic ALS remains a conundrum. Are we missing that lone answer? Missing that elusive common link after years of intensive research appears unlikely. It seems more likely that ALS represents the final common endpoint for a number of different disease processes, or it is truly a multifactorial disease. I suspect that you need a little of factor A (genetic susceptibility), a dash of factor B (environmental exposure), spice it up with a little of C (impaired stress response) and D (misfolded SOD1 protein), and simmer for a period of time with the lid on (to prevent clearance of intracellular inclusions) to create the recipe for ALS.

*Christen Shoesmith
London, Ontario*

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