ANNALS of Clinical and Translational Neurology
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EDITORIAL

Nemesis of neglected neurosarcoidosis

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Annals of Clinical and Translational Neurology 2015; 2(10): 947–948

doi: 10.1002/acn3.247

Neurosarcoidosis (NS) is diagnosed when noncaseating granulomas develop in the nervous system, often associated with similar pathology in other organs.[1] While lung and skin manifestation are more common, the neurological manifestations including meningitis, parenchymal brain or spinal cord lesions, or cranial or peripheral nerve damage are among the most serious and difficult to treat manifestations of sarcoidosis.[2,3] Perhaps because of the difficulty diagnosing NS, variable phenotypes and clinical course, as well as its relative rarity, NS has received shockingly little scientific attention. This is a serious omission, since NS is often disabling and sometimes lethal. Sadly, it is not even truly rare. Indeed, a recent survey of inflammatory brain diseases other than multiple sclerosis at a large medical center identified NS as the second most common inflammatory brain disorder, equal in frequency to neuromyelitis optica.[4] Despite this compelling evidence of the importance of NS, there are virtually no current funded research programs focusing on it.

Given this background, the report of Lareau et al.[5] in this issue of *ACTN* gives hope that NS will become a serious focus for 21st century science. The manuscript reports fine mapping analysis of chromosome 15q25 that implicates the zinc finger gene *ZNF592* in NS. Significant association to a variant in a gene *ZNF592* was found in mapping this region of the genome suspected from a prior genome-wide association study in sarcoidosis. The primary association was defined from a population of 83 African American NS cases compared with 1645 healthy controls. As verification, other variants of this gene were found in an even smaller cohort of European Americans with NS. These findings draw attention to *ZNF592* which seems relevant to the nervous system being widely expressed in the brain as well as having a role in cerebral development. Furthermore, protein associations suggest that this gene may be included in control systems for cellular immunity which would be highly relevant to an immune disorder such as NS. Were this finding replicated in a larger and well-described population, a genetic signature for the population at greater risk of NS could become a valuable research tool, and potentially become clinically useful.

This report is limited by the modest number of documented cases, drawing attention to the dearth of NS studies. At a recent symposium on NS at Washington University in St Louis, scientists gathered to consider research priorities. Collection of a larger cohort of well-documented NS patients was seen as a high priority to initiate more definitive scientific analysis of this problem, empowering more detailed genetic analysis. A larger study that is prospective will also give clearer evidence if phenotypes such as meningeal versus parenchymal NS have unique genetic determinants. Studies seeking evidence of presymptomatic involvement of the nervous system when systemic disease is active elsewhere could also help to identify how distinct NS may be from systemic sarcoidosis, as well as enabling better phenotypic description of the population for genetic study.

Given the paucity of prospective observations, development of clear definitions for NS research is required, as well as prospective collection of biomarker candidates during the course of NS to design appropriately powered randomized treatment studies. MRI scanning is likely to detect lesions with high sensitivity, and reflect their activity by gadolinium enhancement, making it a plausible research marker for disease activity. However, other biomarkers including cerebrospinal fluid (CSF) cells, proteins, sIL2 receptor, and measurements of TNFα and other inflammatory factors may be useful.[6–8] Ultimately, an approach to personalized treatment design based on a firm understanding of the pathophysiology of nervous system disease, combined with biomarkers and genetic profiles, should allow more successful therapy than patients can be offered at present. Prospective collection and analysis of imaging, blood and CSF samples, and

clinical course from well-characterized patients is required to plan realistic randomized intervention trials. An early therapeutic target is likely to test the merits of TNFα inhibitors. Based only on many case reports and small retrospective series, the monoclonal TNFα inhibitor infliximab is frequently recommended for severe brain and spinal cord disease.[9] These trials may require novel design strategies due to the relative rarity of NS. Remarkably, as of 2015, no prospective randomized studies have ever been performed for NS.

As rigorous scientific programs are designed to collect the evidence to better diagnose and manage NS, an emerging genetic framework for NS suggested by Lareau's manuscript will give opportunities to more precisely classify populations for analysis as well as suggest pathophysiological mechanisms relevant to predicting the behavior of the disease and guide therapy. This work should start to banish the nemesis of ignorance that has plagued clinicians seeking to care for patients with NS. It appears that emerging genetic findings, along with increasing power of proteomics, immunologic analysis and imaging are converging to give an opportunity to understand NS much more clearly, and translate this knowledge into more effective therapy for NS patients.

Acknowledgments

The National Institutes of Health (NS 077384) (WUSTL NeuroNEXT, D Clifford PI) supported a conference on neurosarcoidosis held on 24 July 2015 leading to this editorial. Participants contributing to the discussion included Barney Stern and Walter Royal (U Maryland), Wonder Drake and S. Pawate (Vanderbilt), Albert Levin (Henry Ford Health Systems), Jeffrey Gelfand (UCSF), Amy Pruitt (U Penn), Yunxia Wang (Kansas), Carlos Pardo-Villamizar (Johns Hopkins), and Beau Ances and David Clifford (Washington U in St Louis).

Conflict of Interest

None declared.

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