Is “stiff-person syndrome” really autoimmune?

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ABSTRACT

Although its true cause is unknown, Stiff-Person Syndrome (SPS) is considered to be autoimmune, one of the ever-growing list of what now constitutes, according to The National Institutes of Health, more than 80 “autoimmune” diseases. However since SPS remains largely a clinical diagnosis, whose signs and symptoms are non-specific, and mimicked by other disease, its inclusion into autoimmunity has been questioned. Yehuda Shoenfeld’s Infection and Autoimmunity long ago came to the conclusion that all autoimmune diseases were infectious until proven otherwise. Infections themselves are important environmental triggers of autoimmunity, its onset and its severity. Therefore, before a disease can be proclaimed Autoimmune, exhaustive studies must be performed to carefully rule-out infectious disease. The association between immune response to certain mycobacterial infections and autoimmune disease, according to Shoenfeld, has long been suspected. However, a review of the literature shows that this possibility is not being ruled-out, in most cases, by anything beyond a mere acid-fast smear. However, studies have shown that a CSF (cerebrospinal fluid) tubercular acid-fast bacillus (AFB) smear has poor sensitivity (10-15%). In the meantime, disease such as Whipple’s Disease, with its movement disorders, once itself thought to be autoimmune, was found to be caused by an organism related to Mycobacterium avium. Moreover, there is not a sign or symptom in the Stiff-person syndrome and its spectrum that is not found in the literature of neuromuscular phenomena as a result of Central Nervous System mycobacterial infection of the spine and midbrain.

Key words: Stiff-person syndrome, history of stiff-person of syndrome, stiff-man syndrome, autoimmune disease, mycobacteria, Moersch-Waltman syndrome.

INTRODUCTION

Stiff person syndrome (SPS), first described in 1956 in a small series of 14 cases by neurologists Moersch and Woltman (1956), is a rare acquired neurological movement disorder that most often causes progressive muscle stiffness or rigidity which at first predominates in the trunk, slowly progressing to the upper portion of the lower limbs. Such muscular rigidity varies in severity, often accompanied by repeated episodes of severely painful muscle spasms that might cause falls or even respiratory difficulties by interfering with normal muscle contraction, spasms potentially forceful enough to dislocate joints. Such muscle spasms are triggered by a variety of events such as sudden noise, light, physical contact or exposure to cold. Historically both Moersch and Woltman played a significant part in introducing the still controversial electroshock therapy to the Mayo Clinic in May, 1937. Woltman also played an important part in the introduction of insulin therapy at the Rochester State Hospital. In addition, for a time Woltman advocated, in certain select cases, the procedure of frontal lobotomy, which cut the connections to and from the prefrontal cortex of the brain, a then new procedure and concept for that era but today, a disparaged
procedure.

Although the exact cause of Stiff-person Syndrome (SPS) is unknown, many currently think it to be “an autoimmune disorder.” But, at the end of the day, diagnosing a person as having Stiff-person syndrome, initially “nick-named” Stiff-man syndrome, is nothing but a rudimentary, descriptive, observational diagnosis, bolstered to a limited extent by the lab findings of antibodies, mostly directed against the 65-kD form of Glutamic Acid Decarboxylase (GAD65), which might or might not have anything to do with the condition. Such skepticism was expressed early-on by an almost reflexive Editorial in the Journal of the American Medical Association [JAMA] of July 1967, which, shortly after publication, summarily dressed-down Moersch and Woltman’s Stiff-man syndrome. The Editors of JAMA:

“It must be embarrassing for a woman to be told that she is suffering from “stiff-man syndrome” and to be thus made aware that this indeed is a man’s world even in disease. Moersch and Woltman, who first reported the syndrome (1956) in 14 patients afflicted with severe painful muscle contractions, may not have anticipated that the implied ”maleness” in the name they had chosen would often misfire (30%) and the ”stiffness” confuse. If neither maleness nor stiffness define the syndrome, is there a certainty that the syndrome, in fact, exists as a definite entity? Gordon and his associates assure us that it does.” But the Editors of JAMA concluded quite differently, saying: “Can a brief, apt designation for the misnamed syndrome be abstracted from these data and hypothesis? And if it can—a neat trick, to be sure—is it likely to survive probable changes in concepts of mechanisms or etiology that the future may bring? What a pity eponyms [such as Moersch-Woltmann syndrome] are no longer fashionable! Devoid of descriptive content and uncommitted to hypothesis, an eponymic label would obviate much unnecessary stiffness in our concepts of obscure syndromes.”

In addition, as it turns out, the description of a “new” Syndrome for “Stiff-Persons” wasn’t so new after all. It was described in books such as the one edited by John M. Keating, MD long ago. Had Moersch and Woltman done their homework prior to publication, they probably would have had to alter their hypothetical thoughts, or at least have added an important differential diagnosis that was otherwise totally ignored. In Keating’s book, Thirty-two years before Moersch and Woltman saw their first “Stiff-person”, Mary Putnam Jacobi, M.D., a New York Professor of Therapeutics at the Women’s Medical College, described a condition precisely like Moersch’s ‘new’ syndrome of fluctuating rigidity, spasms, and gait disturbance, without calling it “Stiff-man” (Jacobi, 1892). Just as Stiff-man syndrome was known to be of spinal or brainstem origin, the disease Jacobi described could and did attack either.

Jacobi: “These concomitant spinal lesions are the proximate cause of many of the symptoms observed in the course of [a certain] cerebral meningitis, as the stiffness of the trunk, the tetanic attacks [ involuntary muscle cramps or spasms], the contraction and rigidity of the limbs, the jerking and trembling of their muscles; to a considerable extent, even the distribution of the motor and sensory paralysis.” If this sounds like what is now called “Stiff-person Syndrome”, it is only because it accurately describes it. And what was this disease, Mary Jacobi was referring to? It was merely the signs and symptoms of a disease which has been consuming spines for centuries: manifestations of central nervous system tuberculosis of the spine and midbrain.

Jacobi was not alone. Seven years later physician James Young of Philadelphia mentioned a similar disorder as having the same sustained “tetanic” muscular spasms mentioned by Asher in an early 1958 “Stiff-man Syndrome” publication (Asher, 1958), contracts strong enough to cause fractures of the femoral neck, and in one case, the bending of a Smith-Peterson nail. Young’s tubercular muscular spasms were marked by the same involuntary, unpredictable, sustained and often painful muscle contractions found in Stiff-person Syndrome (Young, 1899). Furthermore Young said that not only were such spasms an early hallmark of every joint in the body affected by tubercular disease, but that in the case of the spine, particularly the lumbar region, such painful spasms were one of the earliest diagnostic symptoms of the disease, often involving the paraspinal Iliacus and psoas muscles groups, favored targets of spinal TB whose subsequent distribution of pain mimics the entire spectrum of discomfort encountered in Stiff-person Syndrome.

Dr. De Forest Willard, again writing in the Journal of The American Medical Association (JAMA,) spoke of rigidity of the muscles accompanied by painful spasms, a kind of protective rigidity in the region of the joints and spine affected by tuberculosis (Willard, 1898). In the same article Willard speaks down at practitioners who would mistake tubercular hip or single joint disease for “rheumatism” and therefore not provide proper treatment. As for the defining symptoms upon examination of such joint tuberculosis, “muscular rigidity being one of the earliest and most reliable for the disease.” But the remarkable difficulty of diagnosing spinal tuberculosis, even in low endemicity regions was recently obvious in a study by Raddcliffe and Grant (2021).
Low back pain

Low back pain (LBP) is a ubiquitous health problem, representing one of the most frequent illnesses of mankind. Stiff person syndrome starts with the muscles in the trunk and abdomen. Muscle spasms and stiffness may come and go in its early stages. However, after a while, the stiffness becomes continuous. Muscle stiffness usually begins insidiously in the lower back and legs and can mimic lower back pain, but in time tends to progress to other body parts, mainly to distal limb parts and abdominal muscles. For Stiff-person syndrome to be diagnosed in a patient with chronic, progressive, low back pain is not unusual (Gallien et al., 2002; Bastin et al., 2002), and In the Emergency Room, the diagnosis of SPS can be easily overlooked and misdiagnosed as acute or chronic low back pain.

Although spondylodiscitis, an inflammation of the vertebral spine, the intervertebral disk space, and adjacent soft tissue can have several causes, in many countries, TB is one of its most frequent causes, bolstered, even in developed countries, by immigration trends (Carvalho et al., 2022).

History of the prior invention

The organism[human body] possesses certain contrivances by means of which the immunity reaction, so easily produced by all kinds of cells is prevented from acting against the organism’s own elements and so giving rise to auto toxins ...so that one might be justified in speaking of a "horror Autotoxicus" [the horror of self-toxicity] of the organism. These contrivances are naturally of the highest importance for the existence of the individual. - Paul Ehrlich (Steinman and Nussenzweig, 2002)

Thus, while investigating autoimmunity, the great German bacteriologist and immunologist Paul Ehrlich (1854-1915) rejected the then new hypothesis of autoimmunity: that an organism’s immune system could attack the body’s own tissue, coining it "horror autotoxicus", literally meaning, the horror of self-toxicity. He used this term to describe the body’s innate aversion to immunological self-destruction, insisting that horror autotoxicus itself would prevent such self-toxicity in a living organism.

This was not just any scientist. Ehrlich was an authority on immunology as was Einstein on relativity, and by 1908 he shared a Nobel Prize in Medicine for his work on the immune system. Instrumental in immunology’s very basics, he theorized the very existence of antibodies: proteins with shapes that bind to the proteins that stick out of pathogens, in lock and key fashion. Because of the dualism of specificity of pathogen and host response, the development of modern bacteriology gave rise to the birth of immunology. Thus, Robert Koch paved the way for immunology put forward by his disciple Paul Ehrlich. But Paul Ehrlich had conducted animal experiments which led him to firmly come out against autoimmunity. Animals injected with different species’ blood formed antibodies against such foreign cells, while those injected with the same species did not form disease-causing autoantibodies. To Ehrlich this meant that the immune system would not do something as counterproductive as damaging its own healthy cells, and thus he could not subscribe to this new concept of autoimmunity.

Yehuda Shoenfeld’s Infection and Autoimmunity (2004) long ago came to the conclusion that all autoimmune diseases were infectious until proven otherwise (McDougal, 2006). Infections themselves have long been considered important environmental triggers of autoimmunity, its onset and its severity. But the difference between “trigger” and “cause” sometimes wore thin. And when Shoenfeld revisited the subject in his second edition (2015) of Infection and Autoimmunity he devotes an entire chapter to the concept of Mycobacteria and Autoimmunity, with 13 annotated references (Dubaniewicz, 2015; Tishler and Shoenfeld, 1996; Dubaniewicz, 2013; Dubaniewicz et al., 2013; Dubaniewicz, 2010; Dubaniewicz et al., 2006a, b, c; Cossu et al., 2014; Tasneem et al., 2001; Sheikh et al., 2008; Komiyi et al., 2011; Panchapakesan et al., 1992; Huszti et al., 2004). The association between immune response against mycobacterial infections and autoimmune disease has long been suspected.

In his book Autoimmune Aspects of Lung Disease (1998), Isenberg maintained that not only is tuberculosis itself accompanied by a spectrum of autoantibodies like that seen in autoimmune disease, but that the mycobacteria in general, such as tuberculosis, leprosy, Mycobacterium avium and even the TB vaccination Bacille-Calmette-Guérin can all be accompanied by syndromes resembling diseases conventionally labelled as “autoimmune” (Isenberg and Spiro, 1998). For example, reactivity to the mycobacterial 65 kDa heat shock protein (hsp 65) has been implicated in the pathogenesis of adjuvant arthritis in the rat, and may be involved in the pathogenesis of rheumatoid arthritis or other autoimmune diseases in humans. And that because similar phenomena can be seen in even non-mycobacterial infections (including Lyme disease and syphilis), said Isenberg, “the cause of autoimmune diseases must be questioned.”

The rise and fall of “autoimmune” whipple’s

It is not easy to differentiate an “autoimmune” from an infectious disorder. An instructive case in point is the saga of Whipple’s Disease (WD). At one time, Whipple’s, a rare cause of chronic diarrhea and abdominal pain, easily confused with inflammatory bowel disease such as Crohn’s and Ulcerative colitis, was also thought to be an
autoimmune disease (Weiner and Utsinger, 1986). Movement disorders are a common feature of Whipple’s disease (WD), accounting for half of the cases with neurological symptoms (Bally et al., 2018). As in both Stiff-person syndrome, and mycobacterial central nervous disease, both myoclonus, (myo- “muscle”, clonus "spasm") a medical sign and, generally, not a diagnosis, and dystonia, an actual neurological movement disorder that results in unwanted muscle contractions or spasms can be features of Whipple’s Disease (Méneret et al., 2021). Until the early 1960s, the disease was considered a uniformly fatal and untreatable primary disorder of fat metabolism. But the cause of Whipple’s disease was anything but “autoimmune” and its true origin turned out to be a pathogen related to what Whipple first described in 1907 in a paper in the now-defunct Bulletin of Johns Hopkins Hospital (Dutly and Altwegg, 2001). At that time Whipple reported the isolation of a “Rod-shaped organisms in silver-stained gland tissue, closely resembling the tubercle bacillus”. But it took 100 years, in 2003, to prove that he was right. Using novel diagnostic methods on stored tissue samples from Whipple’s original patient, investigators found T. whipplei, a microbial distant relative of Mycobacterium avium (Fowl tuberculosis), and Mycobacterium paratuberculosis (Dumler et al., 2003). This validated another study wherein as early as 1992, Rook and Stanford insisted that “autoimmune” disease, which at that time included Whipple’s disease, was tied to “conventional mycobacterioses”, such as tuberculosis (Rook and Stanford, 1992).

On “stiff” antibodies

The diagnosis of Stiff-person Syndrome is bolstered to some extent by the lab findings of antibodies, mostly directed against the 65-kD form of Glutamic Acid Decarboxylase (GAD65) enzyme, which might or might not have anything to do with the condition. Since most patients with “classical” SPS have anti-GAD antibodies, it is currently believed that the possible pathological mechanism of SPS is the inhibition of GABA by these anti-GAD antibodies, leading to overexcitation of motor neurons, resulting in continuous muscle rigidity and painful spasms. In actuality, the pancreas needs the enzyme glutamic acid decarboxylase (GAD) to function normally. Antibodies that target this enzyme are called GAD antibodies. This does not automatically make them "autoimmune". And certainly, not all patients with GAD65 antibody in the CSF and the serum will show SPS.

However, long before antibodies directed against GAD65 were considered causative of the then “Stiff-man syndrome”, as well as autoimmune Diabetes Mellitus type 1, it was thought that circulating antibodies against Mycobacterial heat shock protein 65 (hsp65), instigated by stressful condition such as heat, were the true cause of many clinical diseases including the autoimmune diseases (Child et al., 1993, 1995).

Certainly, elevated levels of immune response targeting both GAD 65 and such heat shock protein were both elevated in Diabetes type 1. Then it became obvious that GAD65 and Hsp 65 have substantially similar amino acid sequences (Child et al., 1993). Such similarity between mycobacterial heat shock protein and GAD 65, in and of itself has implicated certain autoimmune disease to be mycobacterial in origin (Naser et al., 2013).

The linkage of what used to be called Stiff-Man Syndrome (SMS) to Diabetes type 1 is undeniable. Insulin-dependent Type 1 diabetes mellitus, also felt to be caused by autoimmune destruction, destroys the insulin-producing beta cells of the pancreas. While most patients with the classical form of ‘Sick-Person Syndrome’ [SPS] have auto-antibodies to GAD, almost all patients positive for this antibody are also positive for islet cell cytoplasmic antibodies and a significant proportion have insulin dependent diabetes.

The results described by Elias et al. (1990) indicate that a beta-cell target antigen in non-obese diabetic (NOD/Lt) mice is a molecule cross-reactive with the 65-kDa heat shock protein (hsp65) of Mycobacterium tuberculosis. Moreover, this tubercular Hsp65 antigen could be used either to induce diabetes, or to vaccinate against diabetes, depending on the form of its administration to pre-diabetic NOD/Lt mice (Elias et al., 1990). A specific role of mycobacterial Hsp’s in the etiology of autoimmune disease is further suggested by the development of adjuvant arthritis in rats following a single injection of an extract of heat killed mycobacterium tuberculosis in Freund’s complete adjuvant (Van Eden, 1990).

Moreover, in as much as one-third of patients, SPS has a focal presentation, limited to rigidity and painful spasms of the trunk or to one limb, (the so-called “focal” SPS). In such cases, which are many, as low as 15% (15-61%) are GAD65 antibody positive. Even classical SPS patients can have, in some studies, only 60% GAD Ab detection, and all of the rest are seronegative or associated with other neural antibodies (amphiphysin, glycine receptor). Add to this the fact that other not directly related neurologic disease can also throw off the very same high titers of these same GAD antibodies, including so-called “autoimmune” cerebellitis, brain stem encephalitis, seizure disorders, and other myelopathies [now neatly swept under the rug as “GAD antibody-spectrum disorders (GAD-SD)"], and one can easily ascertain why Stiff-person syndrome remains a clinical diagnoses, difficult because it is largely based on clinical symptoms.

Preconceived notions/faulty screening

There are problems with the way experimental protocols
Intravenous immunoglobulin (IVIg) is proven to be primarily seeking “autoimmunity”. In fact, it is the sensitivity in most, again, molecular, SF tubercular, even, often with faulty diagnosis and fatal test misses. Such is the rigor gotten is that long

SPS, effective immunotherapy in treat a range of “autoimmune” and inflammatory disorders. with primary antibody deficiencies and, at high doses, to increase the pathogenicity of certain chronic diseases. Intravenous immunoglobulin (IVIg) is used to treat patients with autoimmunity related to the 65-kDa isofrom of glutamic acid decarboxylase (GAD65) antibodies, even if patients with meningeoencephalitis associated with those antibodies have rarely been identified. In the 2023 study “Meningoencephalitis associated with GAD65 autoimmunity”, Kuang et al. (2023), under their infectious disease screening protocols, decided to perform a mere CSF (cerebrospinal fluid) acid-fast (tubercular) stain to detect and thus rule out central nervous system tuberculosis. Unfortunately, such inadequate staining is not an uncommon practice in studies ruling out mycobacterial infection when primarily seeking “autoimmunity.” In fact, it is the norm, and as a result (Sarali et al., 2022), potentially life-saving antibiotics are removed, and IV methylprednisolone, alone, which can spread infection, begun.

Stadelman et al. (2022) concluded that a CSF tubercular acid-fast bacillus (AFB) smear has poor sensitivity in most settings. Thus numerous studies demonstrated low (10–15%) sensitivity for CSF AFB (acid-fast bacilli) smear, which means a significant number of cases are missed using this technique, often with faulty diagnosis and fatal consequences (Seddon et al., 2019). The problem is it happens all the time: in the lab, and in the hospital. Stadelman et al. (2022) instead concluded that at present, the combination of GeneXpert MTB/Rif Ultra (a molecular, rapid diagnostic test that simultaneously detects Mycobacterium tuberculosis complex and rifampicin resistance) and culture present the best chance to diagnose TB meningitis in most settings, although each of these can discover cases that the other test misses. Such is the rigor with which present-day diagnosis should and must be pursued, and even a combination of these tests is far from fool-proof.

**Treatment implications**

Diagnosing a disease as autoimmune has consequences, some of them potentially quite harmful. For example, corticosteroids and other immunosuppressives are used as monotherapy or in combination with other drugs for some SPS patients. These are the same corticosteroids and immunosuppressives that are contraindicated and can even increase the pathogenicity of certain chronic diseases. Intravenous immunoglobulin (IVIg) is used to treat patients with primary antibody deficiencies and, at high doses, to treat a range of “autoimmune” and inflammatory disorders. Intravenous immunoglobulin (IVIG) is proven to be the effective immunotherapy in some, but not all cases of SPS, promoting a clinical improvement for up to 1 year after a standard course of five sessions (Pretorius and Struwig, 2013; Dalakas et al., 2001). But what is forgotten is that IVlg also protects against *M. tuberculosis* infection in a dose-dependent manner. IVlg treatment provides protection even in an established late infection of *M. tuberculosis*.

The beneficial effect of hDLIg against tuberculosis infection was as dramatic as it was unexpected. Administration soon after infection almost completely prevented increases in bacterial numbers, as judged from counts from 40 to 130 days after infection. Later administration, in the stable plateau phase of infection, resulted in a sharp decline in bacterial numbers (Roy et al., 2005).

**Conclusion**

Recently an elaborate explanation has been proposed that even Alzheimer’s is an autoimmune disease (Weaver, 2022). The temptation to declare a disorder as autoimmune obviously becomes more attractive when a definitive pathogen has not been isolated, in this case, again, in the central nervous system. Yet in laboratory animals, Lara-Espinosa et al. (2020) were recently able to effect Alzheimer’s symptomatology through the long arm of immune and not autoimmune phenomena to damage cells in the brain. The investigators created long and short-term memory deficits without having to introduce experimental infection directly into the brain at all. Pando’s group, through the long reach of severe tubercular cell-mediated immunological reactions alone, caused significant amounts of damage to the memory centers in the brain, its neurons and its synapses simply thru initiating a focus of pulmonary tuberculosis in the lungs. They also noted a marked increased synthesis of both inflammatory and anti-inflammatory cytokines in discrete brain areas such as the hypothalamus, the hippocampal formation and cerebellum accompanied by substantial changes in the synthesis of neurotransmitters. In no way was autoimmunity involved. Similarly, in the case of Stiff-man syndrome there is uncertainty as to its pathophysiology and its etiology is also admittedly unknown. Yet exhaustive studies to define an infectious cause has been stifled by labeling it an “autoimmune disorder” when the very definition of this calls for ruling out any and all infectious cause. Until this is done, its cause and possible cure will not be possible.

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