Immunologic Mechanisms Suggested in the Association of
M. pneumoniae Infection and Extrapulmonary Disease:
A Review

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Numerous case reports and retrospective studies suggest an association between M. pneumoniae respiratory infection and extrapulmonary complications, the most common of which involve the central nervous system. There is insufficient evidence based on prospective, carefully controlled observations to confirm this association at the present time. A variety of mechanisms has been suggested to explain the involvement of distant organ systems. These include metastatic infection, autoimmunity, toxin generation, and altered host immunity. While none of these is based on evidence to prove an association, the state of anergy which accompanies M. pneumoniae pneumonia deserves consideration and further study as the most plausible link between infecting organisms and extrapulmonary manifestations.

EVIDENCE OF ASSOCIATION BETWEEN M. PNEUMONIAE
INFECTION AND CENTRAL NERVOUS SYSTEM DISEASE

Epidemiology

Extrapulmonary manifestations have been associated with Mycoplasma pneumoniae infections since Hobart Reiman described neurologic complications in two patients with primary atypical pneumonia in 1938 [1]. Yesnick reviewed this association in 1956 and added one case to the then-existing 38 reports in the literature [2]. Hodges added four case reports in 1972, and in 1973 Lehrer and Kalavsky reviewed 50 reported cases and added five of their own [3,4]. While a variety of extrapulmonary syndromes have been associated with Mycoplasma pneumoniae, central nervous system (CNS) findings are the most frequently reported [5]. Biberfeld's collection of seven patients with well-documented M. pneumoniae pneumonia and neurologic disease is the most impressive example of this association [6]. Since neurologic complications are clinically the most significant and apparent, they will be the focus of this paper.

In addition to case reports and retrospective reviews, two prospective studies have addressed the association of extrapulmonary symptoms and mycoplasma infection. Foy reported no cases among 462 patients with M. pneumoniae pneumonia collected in Seattle over a five-year period [7]. Lind collected 371 patients with CNS findings over a 4½-year period and found evidence based upon serologic analysis of concurrent M. pneumoniae infection in 19 (5 percent), a higher figure than predicted for the incidence of mycoplasma infection in the general population [8].
Taken together, these reports suggest an association between *M. pneumoniae* respiratory infection and neurologic disease. Ponka has reviewed the literature and reported studies of his own from Finland [5]. He estimates the frequency of associated CNS complications to be as high as 4.8 percent but notes that biased selection of cases and non-specificity of serologic reactions employed for diagnosis may have influenced these figures. Other extrapulmonary disease manifestations such as arthritis and carditis occurred somewhat less frequently. If such complications occur in 1 to 5 percent of all patients with *M. pneumoniae* infection, one would have expected several cases of neurologic disease, arthritis, or carditis to have been observed in the Seattle study reported by Foy and colleagues. If the frequency is as low as 0.1 percent as suggested by Yesnick [2], a prospective study would need to accumulate several thousand subjects to yield statistical validity.

**Isolation of Organisms from Extrapulmonary Sites**

Scattered reports of direct isolation of *M. pneumoniae* from blood and cerebrospinal fluid (CSF) have accumulated to support the association of CNS disease with pneumonic infection. Bayer et al. reported evidence of *M. pneumoniae* in CSF and blood of a man with serologically positive *Mycoplasma pneumoniae* and Guillain-Barré syndrome [9]. Although cultures of CSF anduffy coat from peripheral blood were negative, metabolic activity attributable to mycoplasmas was detected by measuring uridine-to-uracil uptake ratios. Such activity, attributed to *M. pneumoniae* by indirect immunofluorescence of inoculated tissue culture cells, was detected on the thirty-first and fifty-fourth days of convalescence, suggesting the organism persistently infected the nervous system for nearly two months. This study, together with other scattered reports of *M. pneumoniae* isolations from extrapulmonary sites [10,11,12], must be considered inconclusive until confirmed by isolation and identification of mycoplasma organisms from extrapulmonary sites in similar cases.

**Autoantibodies**

The presence of autoantibodies to brain and other host tissues has suggested a link between *Mycoplasma pneumoniae* and extrapulmonary disease. Such antibodies are produced during mycoplasma pneumonia and most evidence would suggest they are stimulated by antigens cross-reactive with host tissues, such as the I antigen on erythrocytes and glycolipids in brain tissue. Such antibodies to host tissues have been known since the early descriptions of primary atypical pneumonia, and their common occurrence with uncomplicated *M. pneumoniae* pneumonia would suggest they are not pathogenic for the host in most instances. Rare cases of autoimmune hemolytic anemia have been associated with *M. pneumoniae* infection. Biberfeld's careful study of the association of antibrain antibodies and CNS disease revealed that 80 percent of controls without CNS manifestations had the same type of antibodies [6].

In summary, the evidence of a causal association between *M. pneumoniae* respiratory infection and extrapulmonary disease, particularly of the CNS, is suggestive but not conclusive. Accumulation of more well-documented cases and a stronger epidemiologic association is necessary before organism and disease manifestations can be considered unquestionably linked.
**POSSIBLE MECHANISMS LINKING *M. PNEUMONIAE* INFECTION AND CNS DISEASE**

**Direct Invasion of Organisms**

Given the possibility of this association, what might the mechanisms of interaction be? The nature of *M. pneumoniae* respiratory disease does not suggest that extrapulmonary invasion is likely to occur [13]. The organism is known to attach to the external surface of ciliated mucosal cells, and submucosal penetration is not evident in the experimental animals which have been studied. Neither is systemic escape of *M. pneumoniae* observed in immunosuppressed animals [14]. Nevertheless, organisms have been cultured from blood of patients [11] and, as mentioned above, from spinal fluid [10]. Thus, direct invasion cannot be ruled out. Proof of this mode of pathogenesis would require additional well-documented isolations from spinal fluid or central nervous system tissue as well as evidence of local pathology due to infection. Further careful study of cases, utilizing the more sensitive metabolic detection methods, in addition to culture on standard inert media and tissue culture systems, will be necessary to confirm this proposed etiology of mycoplasma-associated CNS disease.

**Generation of Toxins**

Another mechanism by which *Mycoplasma pneumoniae* in the lung could cause distant CNS manifestations might be through the effect of a soluble toxin. Animal models for this phenomenon are to be found in rolling disease of mice, caused by *M. neurolyticum*, and cerebral arteritis due to *M. gallisepticum* in turkeys; in the latter case, direct infection of cerebral vessels is required to produce disease [15]. *M. pneumoniae* has the ability to lyse red blood cells by generating peroxide, but direct attachment of mycoplasma to erythrocyte is required. Also, the metabolic dysfunction and disruption of cell structure produced by *M. pneumoniae* in tracheal cultures requires attachment of the organism to ciliated epithelial cells [16]. No evidence of a distant toxic effect has been found for *M. pneumoniae*.

**Autoimmunity**

A third mechanism proposed to link *M. pneumoniae* infection and distant CNS disease is the production of autoantibodies. Since a variety of antibodies to host tissues is characteristic of mycoplasma pneumonia, this has been a popular concept. The mechanism by which antibodies to host antigens are formed is not clear, but it is known that infectious agents may modify host tissues and induce autoantibodies. The normal T-lymphocyte suppression of self-immunity can be bypassed by cross-reacting antigens, alteration of host cell antigen by the infecting organism, and non-specific activation of lymphocytes by microbial mitogens. All of these activities are theoretically possible in *M. pneumoniae* infections (as discussed in Symposium VIII: Mycoplasma interactions with lymphocytes and phagocytes). While the presence of autoantibodies is obvious, direct evidence of antibody-mediated injury such as glomerulonephritis or other evidence of immune complex disease has not been described. Biberfeld reported indirect evidence of circulating immune complexes in patients with mycoplasma pneumonia, but this observation has not been confirmed by others [17]. It should also be noted that autoantibodies are present to varying degrees in many human disease states and are more often a secondary manifestation.
than the primary cause of disease. Characteristics of autoimmune disorders such as a tendency to chronicity and a high frequency of certain histocompatibility types have not been associated with extrapulmonary complications of *Mycoplasma pneumoniae* infection. Rather, patients have tended to suffer acute manifestations over a short course and, pending survival of the initial illness, tend not to suffer progressive deterioration. Thus, while autoimmunity cannot be excluded, it appears less likely than other alternatives under consideration.

**Immunosuppression**

Recent advances in defining the immunologic interactions between mycoplasmas and the immune system suggest organism-induced immunosuppression as a mechanism linking extrapulmonary complications with the primary respiratory disease. Biberfeld's observations of anergy to tuberculin skin testing and depressed lymphocyte responses to *M. pneumoniae* antigen during convalescence from acute pneumonia suggest that this is a regular feature of *Mycoplasma pneumoniae* infections [18]. These findings have been confirmed by Sabato et al., who demonstrated depressed stimulation of peripheral lymphocytes by PHA and pokeweed mitogens but not by Concanavalin A [19]. They interpret these results to show a selective decrease in B-lymphocyte function during *Mycoplasma pneumoniae* infection. Whether perturbations of T-lymphocyte suppressor or helper subsets are responsible for this state of immunosuppression remains to be investigated.

Such altered immune responsiveness during mycoplasmal infections could be the permissive factor for several of the associated phenomena under discussion. The escape of organisms from lung tissues to systemic sites, the generation of autoantibodies, and the reported prolonged carriage of organisms in affected tissues could all be facilitated by such a state of anergy. One might even speculate that otherwise quiescent infections of the central nervous system could become activated and produce clinically significant disease manifestations. All of this is, of course, conjectural but certainly careful studies of the immune status of subjects with *M. pneumoniae* pneumonia, with and without extrapulmonary manifestations, are indicated before a link between these entities can be established.

**SUMMARY AND CONCLUSIONS**

In summary, I would like to emphasize the following points relative to this discussion of the nature of associated *M. pneumoniae* infection and CNS disease:

1. That clinical reports suggest an association but that confirmation is lacking at the present time.
2. That altered immune reactivity of the infected host should be considered a possible link between the infecting organism and extrapulmonary complications.
3. That there is a real need for careful study of well-documented cases for evidence of circulating organisms, antigenemia, immune complexes, evidence of localized infection, histopathology, or immunopathology. Only direct evidence, such as culture and identification of organisms and identification of antigen-antibody complexes should be sought, since indirect evidence is abundant but inconclusive. Such studies should also include a careful dissection of the components of the immune response of the infected host to the infecting mycoplasma for evidence of suppression as well as stimulation of immunity.
4. Solution of this complex problem would not only enlighten those interested in human mycoplasmology, it would also provide information relative to the pathogenesis of other infectious diseases in which the infecting organism induces non-specific as well as specific alterations of the host's immune response.

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