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Short Communication

# A Pathway Fundamental to the Progression of Certain Diseases and a Therapeutic Approach

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## Abstract

The hypothesis of a pathway common to progressive forms of multiple sclerosis and some common degenerative diseases, including Alzheimer's disease, Parkinson's disease, and motor neuron disease, is discussed. A three-step pathway is postulated: antigen presentation and immunoglobulin synthesis; activation of the alternate complement pathway and formation of the complement component C3d; and resulting target cell impairment and ultimate death due to microglial activation.

A possible beneficial effect in lessening the rate of decline of these entities by any of the three forms of Interferon-beta or Glatiramer acetate in their usual doses, these inhibiting the antigen-presenting cell; in combination with Azathioprine 50 mg daily to inhibit immunoglobulin synthesis is considered. The addition, in "initial" pilot trials, of intravenous immunoglobulin to such "combination therapies", so as to inhibit the microgliocyte Fc receptor, is thought reasonable.

**Keywords:** Alzheimer's disease; Parkinson's disease; Disease progression; Multiple sclerosis

Alzheimer's disease, Parkinson's disease and motor neuron disease may be primarily immunological entities. Any one of the three preparations of Interferon-beta or Glatiramer acetate, in their usual doses, in combination with Azathioprine 50 mg daily may, for the first time, lessen the rate of decline in some patients with these diseases. The addition of intravenous gamma globulin to the above combinations may, in some, allow responses in "non-responders", or increase the degrees or lengths of responses in "responders".

A "primary" immunological process seems the most plausible explanation of the similarities in histopathology, phenotype and clinical course of the Mendelian genetic and sporadic neurological degenerations; the frequent admixture of two or more histopathological elements of the common neurological degenerations; the frequent association of white matter disease with Alzheimer's disease; and the long-delayed clinical expression of chronic traumatic encephalopathy, in which Alzheimer-like and Lewy-body histopathologies are present [1]. A genetic contribution may "secondarily" induce "antigenicity" [2], in addition to a "primary" deleterious effect.

A beneficial effect of the "combination" of any one of the three preparations of Interferon-beta or Glatiramer acetate in their usual doses, with Azathioprine 50 mg daily, is suggested by the responses to such "combination therapies" of eight patients with progressive forms of multiple sclerosis. Partial and significant reversals of visual and neurological deficits at approximately one year in these patients [3], were maintained for between two-and-a-half years and eight years. (Tables 1A and B). Nevertheless, other patients "responded" for less than one year and some did not "respond" at all.

A "combination" effect was confirmed by studies of visual acuity and Ishihara colour vision scores in a patient with a progressive demyelinating optic neuropathy. Following a progressive five year visual decline, vision was restored to near-normal with "combination therapy", declining when either one of the preparations was withdrawn, returning to near-normal when the "combination" was re-instituted [3], an effect maintained throughout the six years of "combination therapy" (Table 2).

The effects in the eight patients and the patient referred to above were postulated to reflect restitution of function of myelin of axons in areas of "peri-plaque" demyelination. Activated microglia and the complement component C3d were present in these areas in two post-mortem case studies of secondary progressive multiple sclerosis [4]. An identical effect of Interferon-beta or Glatiramer acetate in combination with Azathioprine 50 mg daily in the patient with a demyelinating optic neuropathy suggested an effect common to both preparations, possibly an inhibition of antigen presentation [5]. Azathioprine was presumed to suppress immunoglobulin synthesis. The addition of intravenous

| Patient | Intial | Subsequent | Duration |
|---|---|---|---|
| 1 (VA) | 3/19 , FM | 3/6, 3/4.8 | 8 |
| 1 (CV) | unable to be determined | 2.5/10, 1.5/10 | |
| 2 (VA) | 3/6, 3/4.8 | 3/4.8, 3/3.8 | 2.5 |
| 2 (CV) | 10/10, 10/10 | | |
| 3 (VA) | 3/3, 3.3 | 3/2.4, 3/3 | 3 |
| 3 (CV) | 10/10, 10/10 | 10/10, 10/10 | |
| 4 (VA) | 3/15, 3/15 | 3/12, 3/12 | 3.5 |
| 4 (CV) | 5/10, 4.5/10 | 3.5/10, 7.5/10 | |
| 5 (VA) | 3/3.8, 3/3 | 3/3.8, 3.8 | 5.5 |
| 5 (CV) | 2/10. 2/10 | 8/10, 7.5/10 | |
| 6 (VA) | 3/3.8, 3/15 | 3/4.8, 3/8.5 | 4 |
| 6 (CV) | 10/10, 0/10 | 10/10, 1.5/10 | |
| 7 (VA) | 3/6, 3/15 | 3/3.8, 3/4.8 | 2.5 |
| 7 (CV) | 10/10, 2/10 | 10/10, 6.5/10 | |
| 8 (VA) | 3/4.8, 3/24 | 3/3.8, 3/12 | 3.5 |
| 8 (CV) | 4.5/10, 0/10 | 10/10, 4/10 | |

**Table 1A:** Progressive multiple sclerosis Visual Acuity (VA) and Colour Vision (CV) reversals.

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| Patient | Intial | Subsequent |
|---|---|---|
| 1 | unable to stand | able to run |
| 2 | constant walking stick | occasional walking stick |
| 3 | unable to dorsiflex an ankle | able to dorsiflex the ankle |
| 4 | slurred speech, constant walking stick | normal speech, occasional walking stick |
| 5 | frequent falls, marked urinary urgency | infrequent falls, moderate urinary urgency |
| 6 | absent erections | occasional erections |
| 7 | N/A | N/A |
| 8 | marked urinary urgency, incontinence | slight urinary urgency, nil incontinence |

"N/A" (not applicable) indicates nil neurological reversal.

**Table 1B:** Progressive multiple sclerosis neurological reversals.

| Patient | Intial | Subsequent | Duration |
|---|---|---|---|
| VA | 3/15, 3/4.8 | 3/3.8, 3/3 | 6 |
| CV | 3.5/10, 7/10 | 9/10, 10/10 | |

**Table 2:** Progressive demyelinating optic neuropathy visual acuity and colour vision reversals.

immunoglobulin to such "combination therapies" in these and other patients was postulated possibly to result in additional benefit as intravenous immunoglobulin inhibits the third "arm" of the pathway, activation of the microgliocyte Fc receptor [6].

The sequence: "primary cell or substance" antigen presentation to antigen presenting cell: immunoglobulin synthesis: alternate complement pathway activation and C3d formation: microglial activation by immunoglobulin binding to the Fc receptor: immunoglobulin synthesis amplification by C3d [7]: primary cell damage and resulting antigenicity [2] induced by activated microglia : represents a "positive-feedback" loop that results in "expansion" of the process, such "expansion" expressed clinically as "progression", "progression" the essence of degeneration.

Additionally, genetic "contributions" may be "up-regulated" by activated microglia [8], forming, when present, a second "positive feedback loop".

Activated microglia and C3d are present in Alzheimer's disease, Parkinson's disease, and motor neuron disease [9]. Hence the term "the C3d microgliocytoses", a form of auto-immunity devoid of the usual inflammatory markers, was proposed to describe the nature of progression in the degenerative diseases [10]. The phenotypic expression of individual disease states would then reflect the diminishing physiological contributions, subsequently extinguished, of increasingly impaired and subsequently deceased or "altered", "antigenically-related", neuronal and glial elements.

Stresses imposed by activated microglia upon amyloid-precursor protein in Alzheimer's disease or alpha-synuclein in Parkinsons's disease likely contribute to the formation of neuritic plaques and neurofibrillary tangles in Alzheimer's disease and Lewy bodies in Parkinson's disease. However activated microglia are not necessarily apposed to "target" cells in the degenerative diseases. For instance, activated microglia are not apposed to the Lewy body inclusions of cortical neurons in Lewy body disease. In such cases, a diffuse microgliocytosis [11] may induce a "stressful milieu", detrimental to neurons and glia. A slowly progressive immunological process, consequent upon "induced" neuronal and glial antigenicity, best explains the long-delayed clinical expression of chronic traumatic encephalopathy.

The pathway described above may be a fundamental pathway of disease progression elsewhere in the body. Macrophages, the "systemic counterpart" of microglia, prominent in some slowly progressive diseases, for instance osteo-arthrosis, the latter phase of type 1 diabetes mellitus, the progressive stenosis of cardiac valvular disease, and some forms of cardiomyopathy, may be "causal" rather than "reactive".

Factor H, an "indirect" modulator of C3d formation by its modulation of C3b, and C3d itself appear to contribute to macular degeneration and progressive multiple sclerosis: a polymorphism of Factor H is present in macular degeneration [12]; serum factor H levels [13] and Kynurenine pathway metabolomics [14], the latter reflecting, in part, microglial activation, may be biomarkers of the transformation of the relapsing-remitting form of multiple sclerosis to the progressive.

An almost identical form of "combination therapy" was not beneficial in relapsing- remitting multiple sclerosis [15]. Thus more "acute" forms of disease outside the central nervous system, in which "active", predominantly lymphocytic, inflammation is evident, presumably due to activation of the classical complement pathway, may not respond to such "combination therapies". Responses lasting less than one year or lack of response in some progressive multiple sclerosis patients, referred to above, likely reflect currently unknown or uncertain genetic, environmental or other factors.

The long-term cancer of risk of such "combination therapy" is unknown. Nevertheless, pilot trials in two diseases merit consideration. These are rapidly progressive Alzheimer's disease and rapidly progressive motor neuron disease. Individual measurements of decline rates, before and during therapy, are essential to avoid statistical "clouding" of individual responses. A robust effect, if present, should be evident at one to two years. Ideally, in "initial" pilot trials, intravenous immunoglobulin should be added to the "combination therapies" described above.

Visual acuities determined at different distances and colour vision scores determined by "differing" Ishihara books [3], although psychophysical, are reliable response "markers" in patients with "stable" optic neuropathies of moderate degree due to progressive forms of multiple sclerosis. The initial effect of "combination therapy" in such patients is likely rapid: an initial effect of "combination therapy" upon vision in the patient with a demyelinating optic neuropathy was, according to the patient, present at ten days [3].

If indeed the pathways of progression in progressive multiple sclerosis and the common degenerative diseases are similar or identical, studies of the effects of other preparations, alone or "in combination", in patients with moderate optic neuropathy due to progressive multiple sclerosis, may allow the identification of "candidate" preparations for degenerative disease therapeutic trials.

Clearly, the observations of the author of the effect of "combination therapies" in progressive forms of multiple sclerosis require confirmation by others. The effect of the substitution of Mycophenylate mofetil for Azathioprine might also be elucidated. A possible beneficial effect of Ocrelizumab, beneficial in primary progressive multiple sclerosis [16], in rapidly progressive forms of Alzheimer's disease and motor neuron disease, should also be determined.

Visual Acuities (VA) were measured at 3 m using a National Vision Research Institute "Bailey-Lovie" (logmar) chart. Colour Visions (CV) were assessed using ten Ishihara plates, all containing numbers. Plate contains two numbers, only one number was able to be recognised, the score was recorded as "one half" (0.5). Left-sided values refer to the

right eye, and right-sided values refer to the left eye. "Duration" refers to years of effect.

"Subsequent" values refer to the effect of the addition of Glatiramer acetate or Interferon-beta 1a to Azathioprine 50 mg daily. Withdrawal of any one of these three preparations was followed by a decline to "initial" values. Visual Acuities (VA) were measured at 3 m using a National Vision Research Institute "Bailey-Lovie" (logmar) chart. Colour Visions (CV) were assessed using ten Ishihara plates, all containing numbers. Plate contains two numbers, only one number was able to be recognised, the score was recorded as "one half" (0.5). Left-sided values refer to the right eye, and right-sided values refer to the left eye. Duration refers to years of effect.

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