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Progression of disease and a remedy: Causative role of macrophages and microglia: Remedial effect of immunomodulatory and immunosuppressive therapies ''in combination''

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Summary The possibility of a pathway, common to progression, in entities in which activated macrophages or microglia are present, amenable to particular therapies, is discussed. Immunoglobulin synthesis and activation of the complement pathway may be critical elements in progression.

It is possible progression in a proportion of patients may be lessened by immunomodulatory and immunosuppressive therapies in ''combination'', immunomodulatory therapies inhibiting the antigen presenting cell, and immunosuppressive therapies lymphocyte immunoglobulin synthesis. Such ''combination therapy'' may inhibit more effectively immunoglobulin synthesis and complement pathway activation, thus ''downregulating'' activated microglia or macrophages.

In this perspective, the disease phenotype reflects the particular cell or tissue targeted by activated microglia or macrophages, a form of ''auto-immunity'', devoid of the usual inflammatory markers. Amplification of immunoglobulin synthesis by the complement pathway, particularly the component, C3d, leads to progression of the process.

Diseases in which such ''combination'' therapy might lessen the rate of decline include Alzheimer's disease, Parkinson's disease, multiple sclerosis, macular degeneration, and diabetes.

Why do diseases progress?

Easily understood are mitochondrial cytopathies, in which the more rapid division and increasingly greater proportion of abnormal mitochondria deplete cellular energy supply; storage diseases, in which accumulated materials impair cellular metabolism; and genetically determined impairments of structure, for instance the deficient sarcolemma of Duchenne muscular dystrophy.

Less easily understood are the variable onset of Mendelian genetic conditions and the similarities, in histopathology, phenotype and clinical course,

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of Mendelian genetic and sporadic neurological degenerations.

It has been argued previously that activation of microglia may contribute to progression in certain neurologic degenerations; progression may be the result of immunoglobulin synthesis and complement activation; may be lessened by immunomodulatory and immunosuppressive therapies in ''combination''; and that a therapeutic effect, if present, might reflect the ''combined'' inhibition of antigen presenting cells by immunomodulatory therapies and lymphocyte immunoglobulin synthesis by immunosuppressants [1].

A previous paper describes the therapeutic reversal of a progressive five year visual decline in a patient with presumed demyelinating optic neuropathy, visual acuity restored to near normal with ''combination'' therapy, declining when either one of the preparations was withdrawn, returning to near normal when the combination was reinstituted, an effect maintained to the present, a period of two and half years [2]. Previous publications have described partial and significant reversals of visual and neurological deficits in some patients with progressive forms of multiple sclerosis following the addition of Azathioprine 50 mg daily to any one of the four conventional immunomodulatory therapies in their usual doses [2–4].

The effect was postulated to reflect restitution of function of myelin of axons, previously described in progressive multiple sclerosis at the edge of long standing plaques, an area termed ''periplaque demyelination''. Activated microglia and the complement component C3d present in these areas were thought to be deleterious and likely to contribute to progression [5].

As C3d and activated microgliocytes are present in many of the degenerative diseases, it was suggested the degenerative diseases characterised by activated microgliocytes be termed the ''C3d microgliocytoses'' [1]. It was also suggested a similar pathway resulting in activated macrophages might underlie progression in some systemic diseases, for instances diabetes [6].

To emphasise C3d may be simplistic. Other components of complement may directly activate macrophages [7]; amyloid itself may activate the classical complement pathway [8]; immunoglobulins may directly activate microglia; complement may affect immunoglobulin synthesis [9]; and activation of other parts of the complement system may ''amplify'' the synthesis of alternative ''distal'' components of the complement pathway [10].

Nevertheless, partial and significant reversals of visual and neurological deficits in a proportion of patients with progressive forms of multiple sclerosis have been found to follow the administration of immunomodulatory and immunosuppressive therapies in ''combination'' [2–4]. Interferon-beta and Glatiramer actetate, the latter four amino acids randomly sequenced, both inhibit the antigen presenting cell [11,12]. The interaction of the antigen presenting cell and lymphocyte is an early, fundamental and requisite part of the immune response. Studies in Parkinson's disease [13,14] and motor neuron disease [15] suggest critical contributions to pathogenesis by immunoglobulins and microglia. And C3d amplifies greatly the synthesis of immunoglobulin [16].

Speculatively, to correlate histopathology and clinical course, sudden decline, for instance the relapse of multiple sclerosis, more likely reflects the effects of lymphocytes and membrane attack complex; and gradual decline, for instance, the inexorable progress of the degenerations, the gradual attrition of a target cell by activated microgliocytes.

Admittedly, these are speculations. The effects of ''combination'' therapy in progressive forms of multiple sclerosis need to be confirmed by others. A beneficial effect in the author's experience is present only in a proportion. It is possible the therapeutic outcome reflects the balance between genetically determined ''pro'' and ''anti'' inflammatory factors. For instance, in macular degeneration, a polymorphism in factor H [17], that normally binds complement 3b, rendering inactivated complement 3b susceptible to cleavage by complement factor I [18], might increase levels of the derivatives of C3b, including C3d.

Is it possible such ''combination'' therapy may be beneficial in diseases in which immunoglobulin synthesis is increased but macrophages or microglia are not apparent? Human myasthenia gravis, in which immunoglobulin and membrane attack complex are present at the muscle end plate but macrophages are not, is an example [19]. Experimental models of Friedreich's ataxia do not evidence activated microglia [20]. Yet C3d deposits are present in the dorsal root ganglia of human cases of Friedreich's ataxia (Fig. 1).

Neither stem cell nor gene therapies have, to the present, resulted in a beneficial effect in the degenerations. Current therapies for Alzheimer's and Parkinson's diseases directly or indirectly stimulate receptors on cells destined to die prematurely. But such therapies do not lessen the rate of death of such cells.

If indeed ''combination'' therapy ''down regulates'' the activity of macrophages or microglia, other therapeutic possibilities emerge.

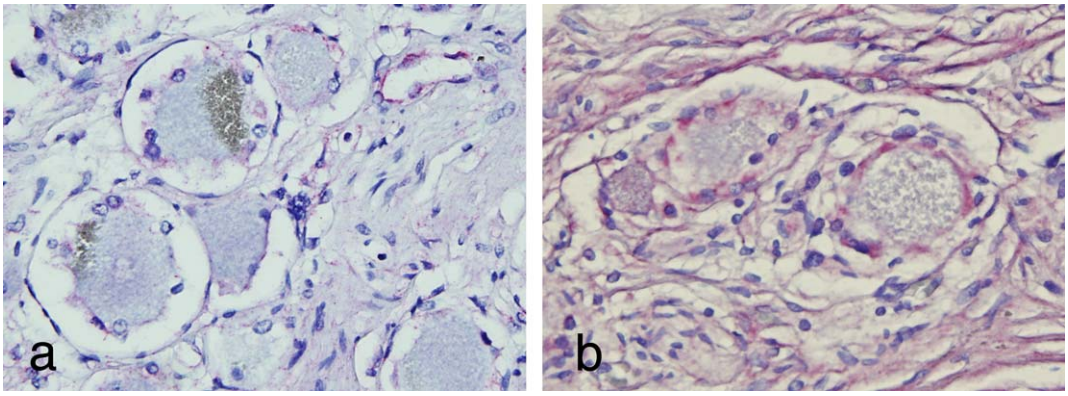

Figure 1 (a) Normal dorsal root ganglion. (b) Friedreich's ataxia dorsal root ganglion (C3d is red, DAKO A0063 rabbit anti-human antibody, ×400).

Atheroma has been designated an ''inflammation'' [21]. Complement deposits are present in atheromatous vessels [22]. Interestingly, the complement component C3d is present in the rarified neuropil of cerebral ''diffuse white matter (Binswanger's) disease'' (Fig. 2).

Activated microglia may contribute to progression in glaucoma [23].

A therapy that inhibits the antigen presenting cell and lymphocyte may allow immunosuppressive preparations of lesser toxicity to be used in transplantation patients.

If activated macrophages contribute to cancer cell proliferation [24], immunomodulatory therapies may prove useful adjuncts to chemotherapy. Urinary paraprotein excretion levels in ''wash in—wash out'' studies in multiple myeloma may allow the possibility to be explored.

Alzheimer's disease, Parkinson's disease, multiple sclerosis, macular degeneration and diabetes likely afflict world wide in excess of two hundred million persons. No therapy thus far has ''robustly'' lessened progression in these entities. ''Combination'' therapy is usually well tolerated. It is conceded the long-term cancer risk, presently thought unlikely to be significant, is unknown.

Surely pilot trials are timely. The author's observations in progressive forms of multiple sclerosis need to be tested by others. ''Combination'' therapy should also be tested immediately in ''pilot'' studies in rapidly progressive forms of Alzheimer's disease and motor neuron disease. If the hypothesis is correct, a robust effect in a proportion of patients may be present at one to two years. Wider studies in these and other conditions might then take place.

Declaration of financial interest

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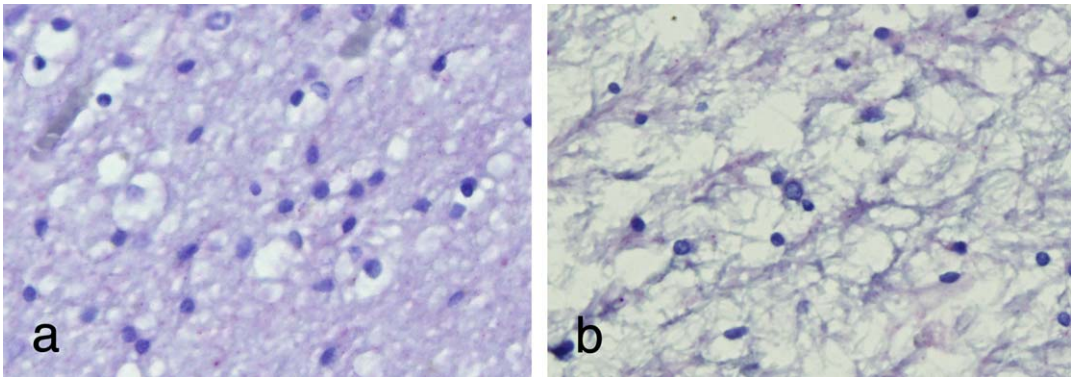

Figure 2 (a) Normal white matter. (b) Diffuse white matter (Binswanger's) disease (C3d is red, DAKO A0063 rabbit anti-human antibody, ×400).

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