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Chapter VI

THERAPEUTIC, PATHOGENETIC AND NOSOLOGIC ASPECTS OF MULTIPLE SCLEROSIS: RELEVANCE TO THE DEGENERATIVE DISEASES

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ABSTRACT

Therapeutic, pathogenetic and nosologic aspects of multiple sclerosis are discussed. "Therapeutic Aspects" describes, following the addition of Azathioprine to immunomodulatory therapies, reversals of visual and neurological deficits in eight patients with progressive forms of multiple sclerosis; regression of uveitis associated with progressive multiple sclerosis in a ninth patient; and reversal of visual deficits in a newly delineated entity, "progressive demyelinating optic neuropathy" in a tenth patient. "Pathogenetic Aspects" highlights the likely importance of complement in the pathogenesis of multiple sclerosis. "Nosologic Aspects" discusses conceptual difficulties in the present classification of relapsing-remitting and progressive disease. The wider import of these observations and pathogenetic considerations is considered in the fourth section, "Relevance to the Degenerative Diseases".

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THERAPEUTIC ASPECTS

Introduction

Disability in the progressive forms of multiple sclerosis has been held to be irreversible [71]. The case reports below describe partial and significant reversals of visual and neurological deficits in eight patients with progressive forms of multiple sclerosis, following the addition of Azathioprine to any one of the four conventionally used immunomodulatory therapies. Such therapy is henceforward referred to as "combination therapy". Regression of uveitis in a patient with multiple sclerosis and uveitis with "combination therapy" is the subject of the ninth case report. The tenth case documents reversal of visual deficits by "combination therapy" in a newly delineated entity, "progressive demyelinating optic neuropathy".

Therapies Received in Patients 1-8

All patients had commenced prior one of the following four immunomodulatory therapies: Glatiramer acetate 20mg by subcutaneous injection daily; Interferon beta-1b 8 million units (unless otherwise stated) by subcutaneous injection second daily; Interferon beta-1a 44 microgrammes (unless otherwise stated) by subcutaneous injection three times weekly; or Interferon beta-1a 30 microgrammes once weekly by intramuscular injection. The dose of oral Azathioprine added was 25mg daily, increasing after one week to 50mg daily.

Visual Parameters

Visual acuity denominators with the numerator "3" refer to acuities measured at 3 meters using a National Vision Research Institute "Bailey-Lovie" (logmar) chart. Acuities were measured without and with pinhole. The better reading was that recorded. Colour visions were assessed using ten (10) Ishihara plates, all containing numbers. Where in a plate containing two numbers, only one number was able to be recognised, the score was recorded as "one half" (0.5). Where only one number in two, of two or more plates, was able to be recognised, the "half" scores were "summed". For visual acuities and Ishihara scores, "R" denotes right and "L" left.

Responses of Patients 1-8

Reversals in all patients were gradual and progressive, usually with onset at two to four weeks, reaching a maximum at two to four months.

Primary progressive, progressive relapsing and secondary progressive cases responded similarly to the addition of Azathioprine. The effects of the addition of Azathioprine to any one of the four immunomodulatory therapies were unable to be distinguished.

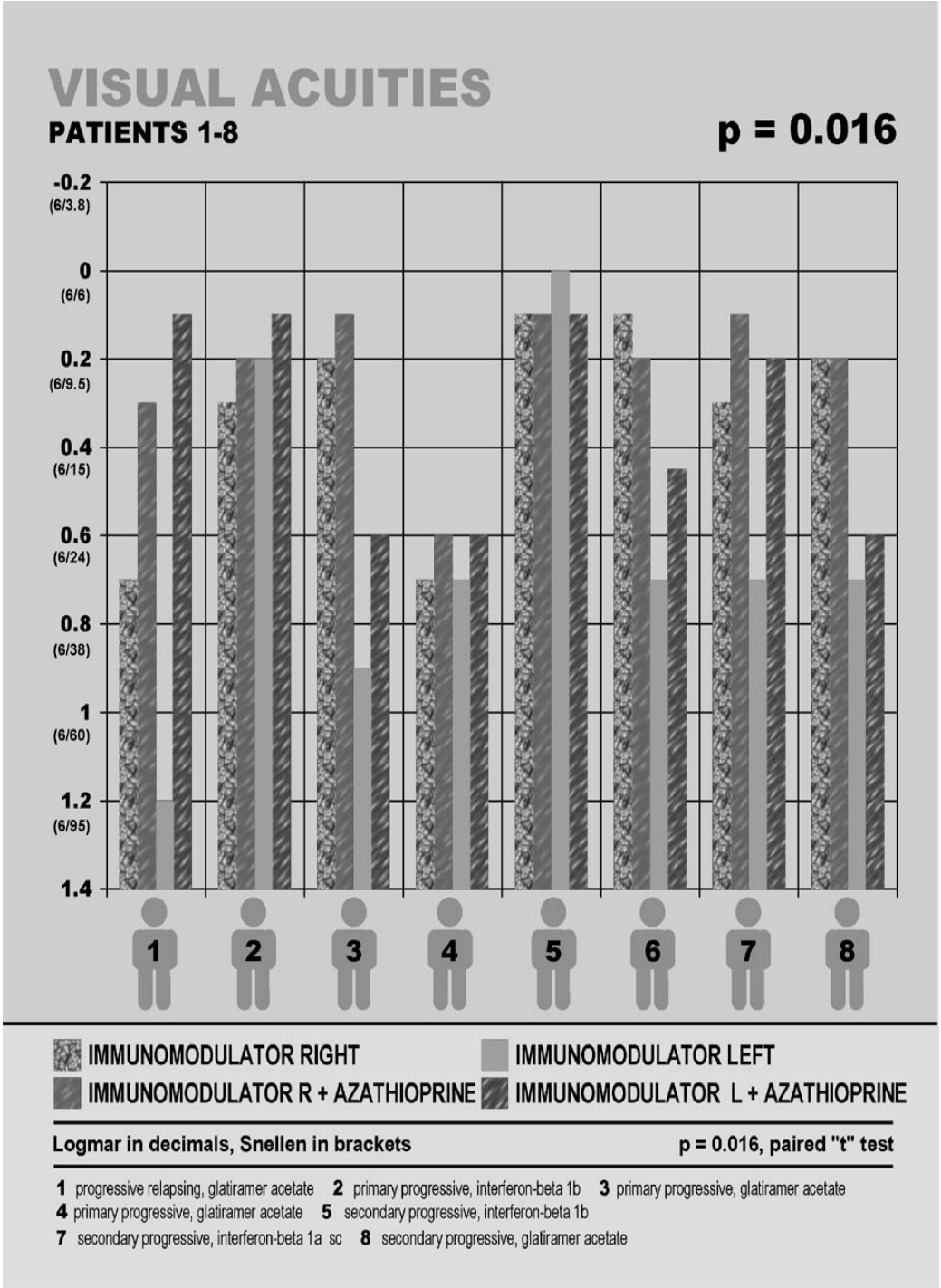
VISUAL ACUITIES
PATIENTS 1-8
p = 0.016
-0.2 (6/3.8)
0 (6/6)
0.2 (6/9.5)
0.4 (6/15)
0.6 (6/24)
0.8 (6/38)
1 (6/60)
1.2 (6/95)
1.4
1
2
3
4
5
6
7
8
IMMUNOMODULATOR RIGHT
IMMUNOMODULATOR LEFT
IMMUNOMODULATOR R + AZATHIOPRINE
IMMUNOMODULATOR L + AZATHIOPRINE
Logmar in decimals, Snellen in brackets
p = 0.016, paired "t" test
1 progressive relapsing, glatiramer acetate
2 primary progressive, interferon-beta 1b
3 primary progressive, glatiramer acetate
4 primary progressive, glatiramer acetate
5 secondary progressive, interferon-beta 1b
7 secondary progressive, interferon-beta 1a sc
8 secondary progressive, glatiramer acetate

Figure 1.

Presentation of Results

Visual acuity and Ishihara scores are depicted in figures 1 and 2 respectively.

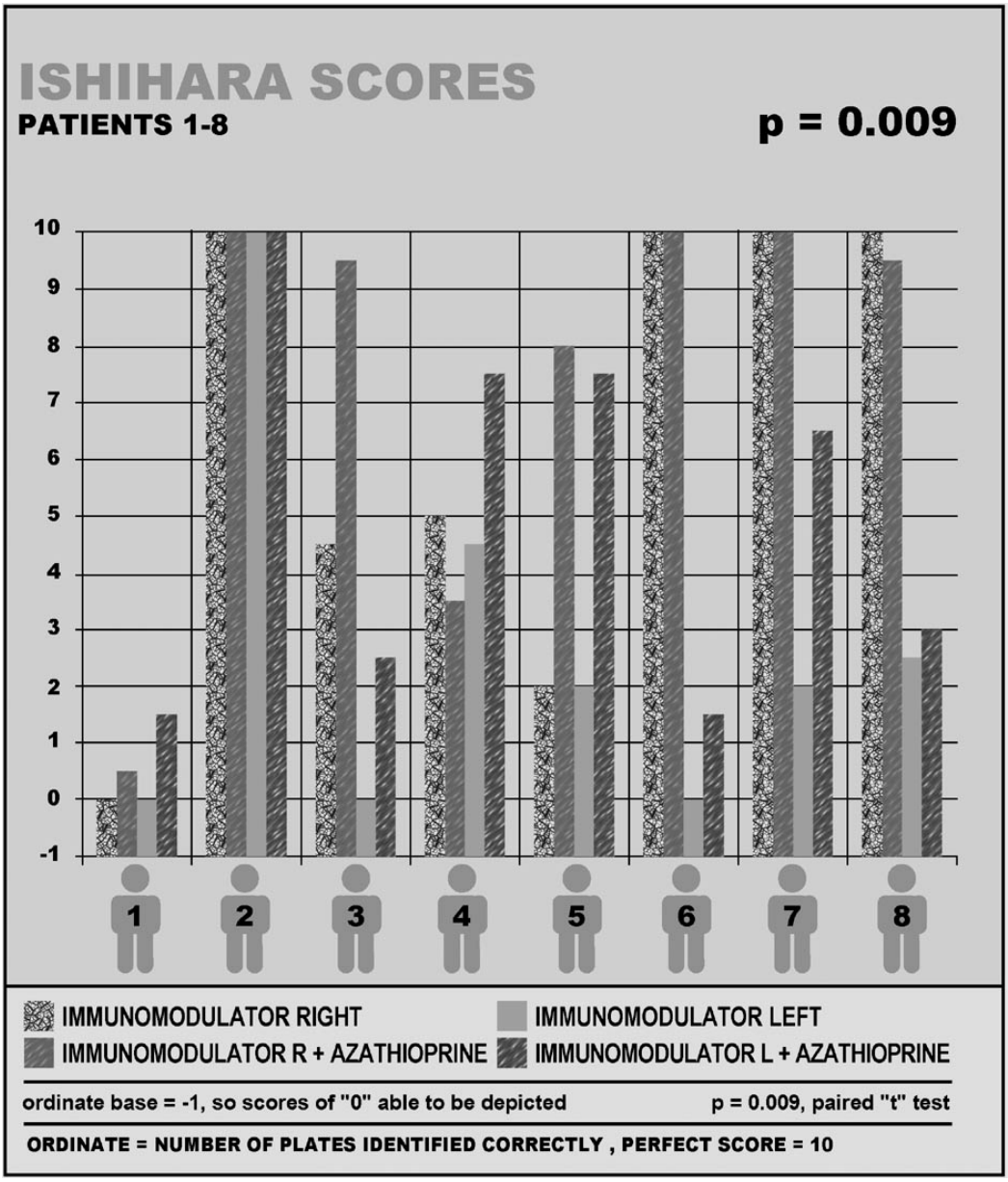

Figure 2.

Case Reports

Case 1 - Progressive Relapsing (Described Previously) [45]

A 24 year old woman suffered progressive relapsing multiple sclerosis. She developed during the previous year and a half fluctuating and progressively increasing visual and cerebellar deficits. The minimum visual acuities were 3/19 on the right and the perception of finger movement at 1 meter on the left. Television images were perceived as "black and white". Ishihara scores were not determined at that time. She became able to walk only with a wide base and with support on either side. Urinary urgency and incontinence were present. A neuropsychologic assessment evidenced impairments of problem solving abilities and attention. Azathioprine was added to Glatiramer acetate.

Eight months after, the visual acuities were 3/6 R and 3/4.8 L. Television images were perceived "in colour". She was able to jog one half kilometre without difficulty. Slight difficulties in standing on either foot unsupported and in the execution of tandem gait were present. Micturition was normal. Neuropsychologic assessment after nine months suggested improvements in attention and speed of information processing.

Case 2 - Progressive Relapsing Multiple Sclerosis

A 46 year old woman suffered primary progressive multiple sclerosis, commencing at age 39. The visual acuities were 3/6 R and 3/4.8 L. The Ishihara scores were 10/10 R and 10/10 L. She was unable at all to dorsiflex the left ankle against gravity. Delay in the initiation of micturition was present constantly. Fatigue was marked. A walking stick was usually required. Azathioprine was added to Interferon beta-1b.

A year and a month after, the visual acuities were 3/4.8 R and 3/3.8 L. The Ishihara scores were 10/10 R and 10/10 L. She was able to dorsiflex the left ankle against gravity to two thirds of its normal excursion. Micturition was initiated promptly on one of five occasions. Fatigue was mild. A walking stick was required infrequently.

Case 3 - Primary Progressive Multiple Sclerosis

A 52 year old man suffered primary progressive multiple sclerosis, commencing at age 46. The visual acuities were 3/3 R and 3/3 L. The Ishihara scores were 10/10 R and 10/10 L. He was unable to dorsiflex the right ankle at all against gravity. He was unable at all to execute tandem gait. Pain and numbness within the soles of the feet were present. Urgency of micturition was moderate. Fatigue was moderate. Azathioprine was added to Glatiramer acetate.

A year and two months after, the visual acuities were 3/2.4 R and 3/3 L. The Ishihara scores were 10/10 R and 10/10 L. He was able slightly to dorsiflex the right ankle against gravity. He was able to execute tandem gait with slight difficulty. Pain and numbness within the soles of the feet were less marked. Urgency of micturition was slight. Fatigue was moderate.

Case 4 - Primary Progressive Multiple Sclerosis

An 18 year old woman suffered primary progressive multiple sclerosis, commencing at age 14. The visual acuities were 3/15 R and 3/15 L. The Ishihara scores were 5/10 R and 4.5/10 L. Colors of traffic lights were unable to be perceived. Speech was slurred and slow. Incoordination of the upper limbs was marked: she was unable to hold a glass in mid-air. She used a "walker" at all times at home. Urinary urgency and incontinence were marked. Faecal incontinence was present. Marked fatigue was present. Azathioprine was added to Glatiramer acetate.

A year and a half after, the visual acuities were 3/12 R and 3/12 L. The Ishihara scores were 3.5/10 R and 7.5/10 L. Colors of traffic lights were able to be perceived. Speech was normal. Incoordination of the upper limbs was less marked: she was at times able to hold a glass in mid air. She used a walking stick at home. She was able at times to walk without assistance. Urinary urgency and incontinence were markedly reduced. She was no longer incontinent of faeces. Fatigue was moderate.

Case 5 - Secondary Progressive Multiple Sclerosis

A 50 year old woman suffered secondary progressive multiple sclerosis, commencing at age 43, progressive at age 48. The visual acuities were 3/3.8 R and 3/3 L. The Ishihara scores were 2/10 R and 2/10 L. She was "fatuous" and garrulous. Tandem gait was unable to be executed. She fell frequently. Urinary urgency was marked. Urinary incontinence was present once monthly. Probantheline bromide was required. Fatigue was moderate. Azathioprine was added to Interferon beta-1b.

A year and nine months after, the visual acuities were 3/3.8 R and 3/3.8 L. The Ishihara scores were 8/10 R and 7.5/10 L. She appeared more "sensible" and less talkative. Tandem gait was able to be executed with slight difficulty. She fell infrequently. Urgency of micturition was moderate. She was no longer incontinent of urine. She no longer required Probantheline bromide. Fatigue was moderate.

Case 6 - Secondary Progressive Multiple Sclerosis

A 60 year old man suffered secondary progressive multiple sclerosis, commencing at age 42, progressive at age 46. The visual acuities were 3/3.8 R and 3/15 L. The Ishihara scores were 10/10 R and 0/10 L. He was wheelchair bound and required a suprapubic catheter. He required assistance to move in bed. Erections had been absent during the previous 8 years. Azathioprine was added to interferon beta-1a.

One year and two months after, the visual acuities were 3/4.8 R and 3/8.5 L. The Ishihara scores were 10/10 R and 1.5/10 L. He was able to move about more easily when in bed. Occasional short lasting incomplete erections were present weekly. He remained wheel chair bound and continued to require a suprapubic catheter.

Case 7 - Secondary Progressive Multiple Sclerosis

A 60 year old woman suffered secondary progressive multiple sclerosis, commencing at age 48, progressive at age 59. The visual acuities were 3/6 R and 3/15 L. The Ishihara scores were 10/10 R and 2/10 L. Urinary urgency was moderate. Fatigue was moderate. Azathioprine was added to Interferon beta-1a, 22 microgrammes, by subcutaneous injection.

One year after, the visual acuities were 3/3.8 R and 3/4.8 L. The Ishihara scores were 10/10 R and 6.5/10 L. Urinary urgency was slight. Fatigue was moderate.

Case 8 - Secondary Progressive Multiple Sclerosis

A 27 year old man suffered secondary progressive multiple sclerosis, commencing at age 22, progressive at age 23. The visual acuities were 3/4.8 R and 3/24 L. The Ishihara scores were 4.5/10 R and 0/10 L. Numbness within the feet was moderate. Urgency of micturition was marked. Incontinence of urine was present approximately 4 times yearly. He required Oxybutynin hydrochloride. Fatigue was marked. Azathioprine was added to Glatiramer acetate.

A year after, the visual acuities were 3/3.8 R and 3/12 L. The Ishihara scores were 10/10 R and 4/10 L. Numbness within the feet was slight. Urgency of micturition was slight. He was no longer incontinent of urine. He no longer required Oxybutynin hydrochloride. Fatigue was mild.

Discussion of Cases 1-8

These case histories describe the partial and significant reversal of visual and neurological deficits in progressive forms of multiple sclerosis in eight patients following the addition of Azathioprine to immunomodulatory therapies. Reversals were documented in the following parameters: visual acuity; colour vision; cerebellar, pyramidal and sensory functions; bladder and bowel control; fatigue; behaviour and cognition.

Primary progressive, progressive relapsing and secondary progressive cases responded similarly. The effects of the addition of Azathioprine to any one of the four immunomodulatory therapies were unable to be distinguished. Nevertheless, with the exception of case 1, reversals did not alter EDSS (Expanded Disability Status Scale) scores.

The eight cases form part of a group of 33 patients with progressive disease. Twenty one were felt to have 'reversed" in one or more parameters, six were unchanged, and six continued to deteriorate. The periods of observation were between eleven and twenty seven months.

The index case is felt to reflect disease, affecting particularly optic nerve and cerebellar fibers, sparing, in the main, spinal cord pyramidal tract fibers, with disease "arrest" due to therapy applied relatively early in the course. Slight reductions in visual acuities following the addition of Azathioprine in patients 2, 5 and 6 are felt to reflect "natural" variations in visual acuity or the "perturbations" inherent in auto-immune disease, rather than a detrimental effect of Azathioprine.

In relapsing-remitting disease, Interferon beta-1b [29], Interferon beta-1a [52, 31] and Glatiramer acetate [32] reduce relapse rate and disability burden, while Azathioprine as a single agent is no more, and possibly less, effective than immunomodulatory therapies [74].

Studies in relapsing-remitting disease suggest a beneficial effect of Azathioprine when added to immunomodulatory therapies: Azathioprine 50 mg daily added to Interferon beta-1A administered intramuscularly once weekly and low dose steroids reduced the relapse rate by 69% in 42 patients at two years; [24] Azathioprine 100 to 200mg daily added to Betaferon beta-1b in six patients reduced by 69% the number of Gadolinium-enhancing lesions at 15 months [43]. Azathioprine 50 to 250 mg daily added to Interferon beta-1A administered

subcutaneously second daily in 23 patients reduced the relapse rate, extent of increase in EDSS scores, and the number of new lesions detected by T1 and proton density-T2 weighted sequences at two years [40].

Nevertheless deficit "reversals" were not described in these studies.

Might then the severity of the "attack" leading to a relapse in relapsing-remitting disease be more intense, less easily able to be suppressed than less severe "disruptions" in progressive disease. A lesser degree of disruption of the blood-brain barrier in progressive disease, as evidenced by serial Gadolinium-enhanced magnetic resonance image scans [62], supports this possibility.

Gradual and partial restoration of function, commencing at two to four weeks, reaching a maximum at two to four months, suggests a beneficial effect upon the physiology, and possibly morphology of, myelin [54] rather than an effect upon "local" factors [60, 69] or axonal mechanisms [17], likely to reach a "plateau" in the shorter term. In the absence of direct evidence, the nature of the process remains conjectural.

Failure to restore to normal tandem gait and to reverse failure of visual suppression of the vestibulo-ocular reflex indicates the effect is suppression, not cure. Failure to reverse internuclear ophthalmoplegia may reflect the susceptibility of densely myelinated tracts, such as the medial longitudinal fasciculus, to repeated demyelination [55], and thus axonal loss.

Neuropathologic studies in secondary progressive multiple sclerosis indicate a substrate for deficit reversal. Disrupted myelin, "activated' microgliocytes and the complement component, C3d, were found at the edge of long standing plaques. The deposition upon myelin of C3d, able to amplify greatly antigen immunogenicity, was felt to lead to increased numbers of "activated" microglia. Such "periplaque demyelination" was felt likely to contribute to "progression" in secondary progressive disease [56].

The effect of Azathioprine when added to immunomodulatory therapies, an effect not present with immunomodulatory or immunosuppressive therapies alone, suggests therapeutic actions at separate sites. As the effects of any one of the four immunodulatory therapies when added to Azathioprine were unable to be distinguished, an effect common to these therapies, possibly inhibition of the dendritic (antigen presenting) cell [28], may be responsible. Immunosuppressive therapies are likely to suppress sequentially lymphocyte activation, immunoglobulin synthesis and activation of the complement cascade, lessening the formation of C3d.

A cautionary note: in a previous study in patients with secondary progressive disease, EDSS scores increased rather than decreased after the addition of Azathioprine to Interferon Beta-1b [20]. "Reversals" were not documented.

The present observations indicate that, to the contrary, in some progressive patients, "fixed" deficits of all types, are, at least in the short and medium terms, partially reversible. Clearly, controlled clinical trials, preferably in patients in the early stages of progressive disease, are required. The possibility of further improvement with the addition of intravenous gamma globulin, able to inhibit the complement cascade and thus microgliocyte activation [3, 68], might also be determined.

An additional cautionary note: although Azathioprine increases the risk of cancer only slightly [69], the long term cancer risk of "combination therapy" remains unknown.

Case 9 - Primary Progressive Multiple Sclerosis and Uveitis

A 41 year old woman suffered primary progressive multiple sclerosis, commencing at the age of 30. An associated uveitis required oral Prednisolone 25mg once weekly. The visual acuities were 3/7.5 R and L. She was able to identify 10/10 Ishihara plates R and L. Azathioprine was added to Glatiramer acetate.

A year after, the visual acuities were 3/6 R and 3/3.8 L. She was able to identify 10/10 Ishihara plates R and L. Her uveitis regressed and was considered by the attending ophthalmologist to be "quiescent" She no longer required oral Prednisolone.

Discussion of Case 9

Regression of uveitis in the absence of steroidal therapy , not possible for many years, was considered by the attending ophthalmologist to be likely the result of combination therapy and not Azathioprine alone.

Regression of uveitis cannot be ascribed to an effect upon myelin. The response suggests "combination therapy" may exert a greater anti-inflammatory effect than steroidal or immunosuppressive therapy alone and thus may "allow" the use of lower dose, less "potent" or less "toxic" immunosuppressive medications.

Case 10 – Progressive Demyelinating Optic Neuropathy: Therapeutic Reversal of a Newly Delineated Entity

Introduction

Optic neuropathy may be genetic, mitochondrial, immunologic, toxic, nutritional, compressive or vascular in origin. Where such factors are unable to be discerned, the term "idiopathic" optic neuropathy is applied. In the periphery, "idiopathic" axonal polyneuropathy does not respond to therapeutic interventions [70] but "idiopathic" demyelinating polyneuropathy may [58]. Thus a distinction between primarily axonal and primarily demyelinating processes in "idiopathic" optic neuropathy seems reasonable.

The present report describes, for the first time, a case of progressive, presumably demyelinating, optic neuropathy in which vision in the more severely affected eye clearly improved when either Interferon-beta 1a (by intramuscular injection) or Glatiramer acetate (by subcutaneous injection) was combined with low dose oral Azathioprine but not when any one of the three preparations was administered alone.

Case Report

A 46 year old woman suffered gradually diminishing vision, on the right hand side in the previous six years, and on the left hand side in the previous sixteen months. "Flashes" of light (phosphenes) were present intermittently. Vision allegedly deteriorated further with hot showers and baths and in hot and humid weather. Orbital discomfort unaffected by eye movement was present bilaterally. The past and family histories were not contributory.

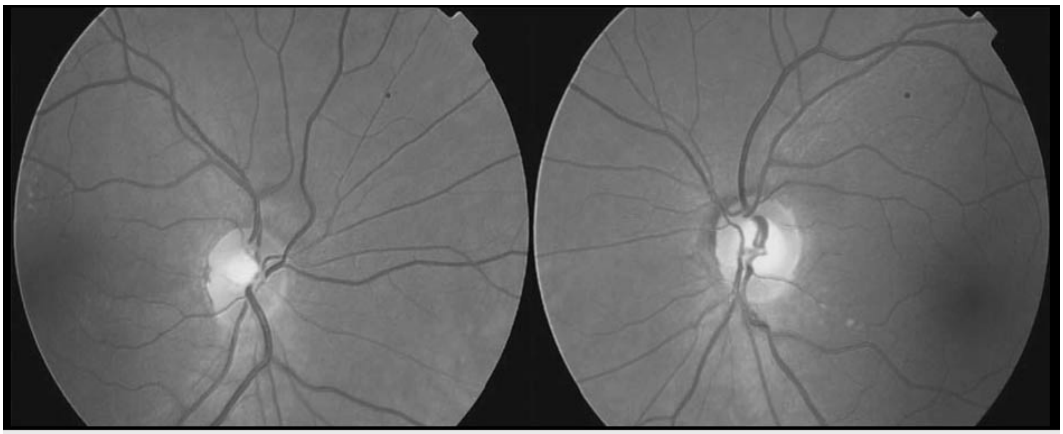

Figure 3.

The visual acuities were 3/15 R and 3/6 L. She was able to identify 3.5/10 Ishihara plates R and 6.5/10 Ishihara plates L. The temporal aspect of the right optic disc was slightly pale. The left optic disc was normal. (figure 3) The retinal nerve fiber layers were normal. Automated perimetry evidenced slight reductions in scores in the temporal field of vision of the right eye and the nasal field of vision of the left eye. Contrast sensitivity scores were below normal, more markedly on the right hand side. The neurologic examination was normal.

Relevant hematologic, biochemical, serologic (including ACE) and tumour marker indices were normal. Full and half field visual evoked responses were normal. Multifocal visual evoked response latencies were normal. CT scans of the chest, abdomen and pelvis and Gadolinium enhanced magnetic resonance image scans of the orbits and brain were normal.

Visual Analyses

Vision was assessed sequentially at the following times and under the following conditions:

1. at "0" weeks, without any medication (baseline, also termed "nil")
2. at 6 weeks, after the commencement of Interferon-beta 1a, 30 ug by intramuscular injection once weekly, at "0" weeks (effect of interferon-beta 1a alone)
3. at 9 weeks, after the addition of Azathioprine 50mg daily at 6 weeks (effect of interferon-beta 1a and Azathioprine)
4. at 12 weeks, after the discontinuation of Interferon beta-1a at 9 weeks, after which only Azathioprine 50mg daily was received (effect of Azathioprine alone)
5. at 15 weeks, after the addition of Glatiramer acetate 20mg by subcutaneous injection daily at 12 weeks to Azathioprine 50mg daily (effect of Glatiramer acetate and Azathioprine)
6. at 19 weeks, 4 weeks after the discontinuation of Azathioprine at 15 weeks, after which only Glatiramer acetate 20mg by subcutaneous injection daily was received (effect of Glatiramer acetate alone)

Visual acuities were measured at 6 meters with a Snellen chart and at 3 meters and 8 feet using National Vision Research Institute "Bailey-Lovie" (logmar) charts. Acuities were measured without and with pinhole. The better reading was that recorded. Acuities in conditions 2-6 were also measured by a four-alternative "forced choice" paradigm, minimally affected by attention and motivation [67], nevertheless expressing at times a value different to conventional techniques [51].

Color visions were assessed with two books, one containing 10 Ishihara plates and the other 17 Ishihara plates. For Ishihara scores, where in a plate containing two numbers, only one number was able to be recognised, the score was recorded as "one half" (0.5). Where only one number in two, of two or more plates, was able to be recognised, the "half" scores were "summed". To allow comparisons between books, Ishihara scores indicating the number of plates correctly identified were expressed as a percentage.

Automated perimetry scores (Humphrey 24/2), contrast sensitivities, full and half field visual evoked responses and multifocal visual evoked responses were determined in each condition.

"R" denotes right and "L" denotes left.

Statistical determinations were by analyses of variance.

As "forced choice" visual acuity values were not determined at "baseline", statistical analysis for visual acuities was limited to conditions 2-6.

Responses to Therapies

Visual acuities in the more severely affected right eye clearly improved when either Interferon-beta 1a or Glatiramer acetate was combined with Azathioprine but not with any one of the three preparations alone ($p < 0.001$, figure 4).

Ishihara scores in the more severely affected eye clearly improved when Interferon-beta 1a, 30 ug by intramuscular injection weekly was combined with oral Azathioprine 50mg daily ($p < 0.005$, figure 5). A definite improvement in color vision when Glatiramer acetate 20mg by subcutaneous injection daily was combined with oral Azathioprine 50mg daily was unable to be demonstrated.

Full and half field and multifocal visual evoked response latencies and contrast sensitivity and automated perimetry scores did not change significantly throughout. Contrast sensitivity scores, subnormal in all conditions, tended to increase at higher frequencies with "combination therapy", but did not correlate reliably with improvements in visual acuities.

Neutralising antibodies to interferon-beta were undetectable throughout.

The onset of effect, according to the patient, was 10 days after the commencement of any one of the second medications. It was described as "progressively increasing clarity and brightness".

Orbital pain and phosphenes resolved completely with combination therapy and returned after withdrawal of any one of the medications.

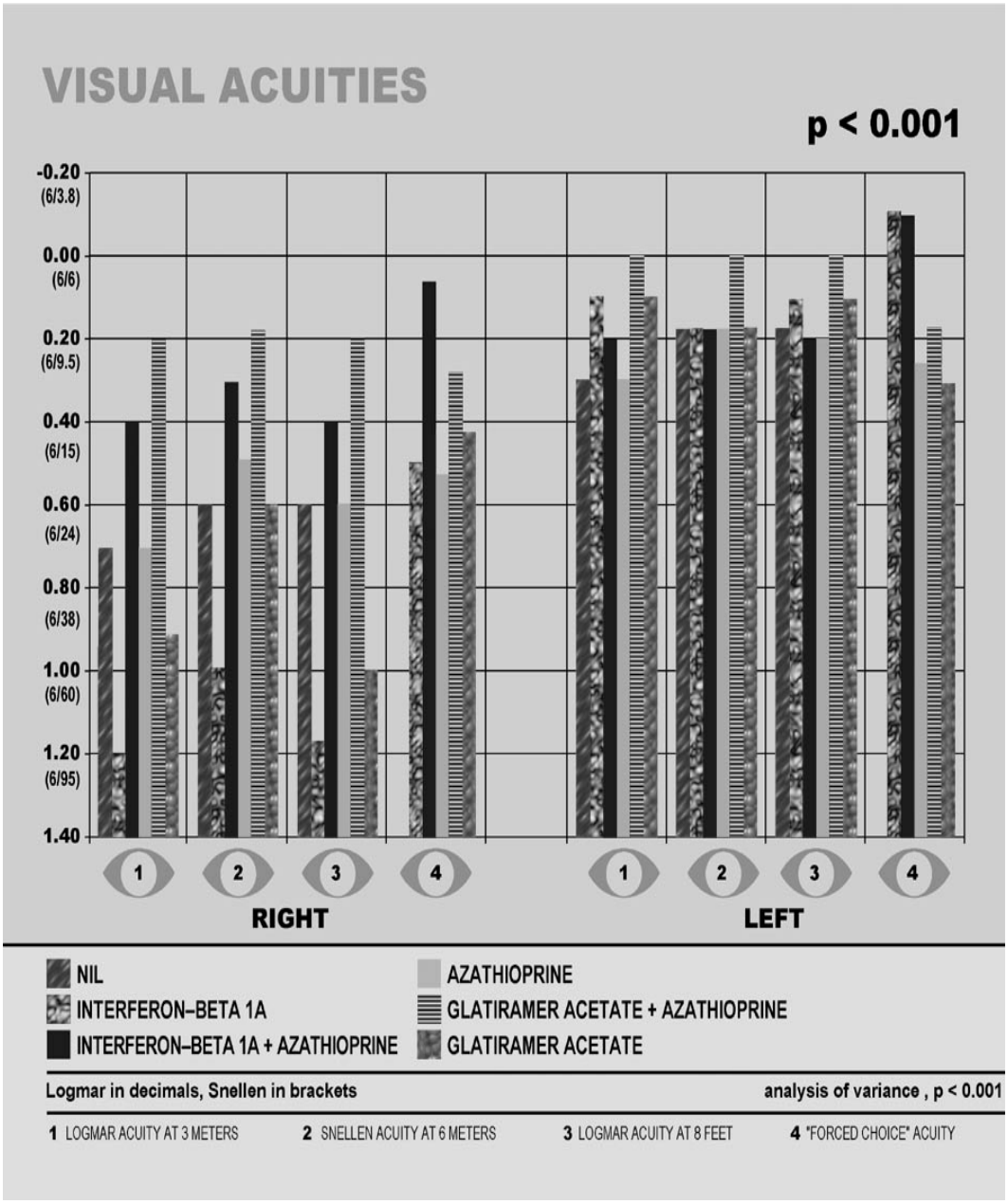
VISUAL ACUITIES
p < 0.001
-0.20 (6/3.8)
0.00 (6/6)
0.20 (6/9.5)
0.40 (6/15)
0.60 (6/24)
0.80 (6/38)
1.00 (6/60)
1.20 (6/95)
1.40
1 2 3 4
RIGHT
1 2 3 4
LEFT
NIL
INTERFERON–BETA 1A
INTERFERON–BETA 1A + AZATHIOPRINE
AZATHIOPRINE
GLATIRAMER ACETATE + AZATHIOPRINE
GLATIRAMER ACETATE
Logmar in decimals, Snellen in brackets
analysis of variance , p < 0.001
1 LOGMAR ACUITY AT 3 METERS
2 SNELLEN ACUITY AT 6 METERS
3 LOGMAR ACUITY AT 8 FEET
4 "FORCED CHOICE" ACUITY

Figure 4.

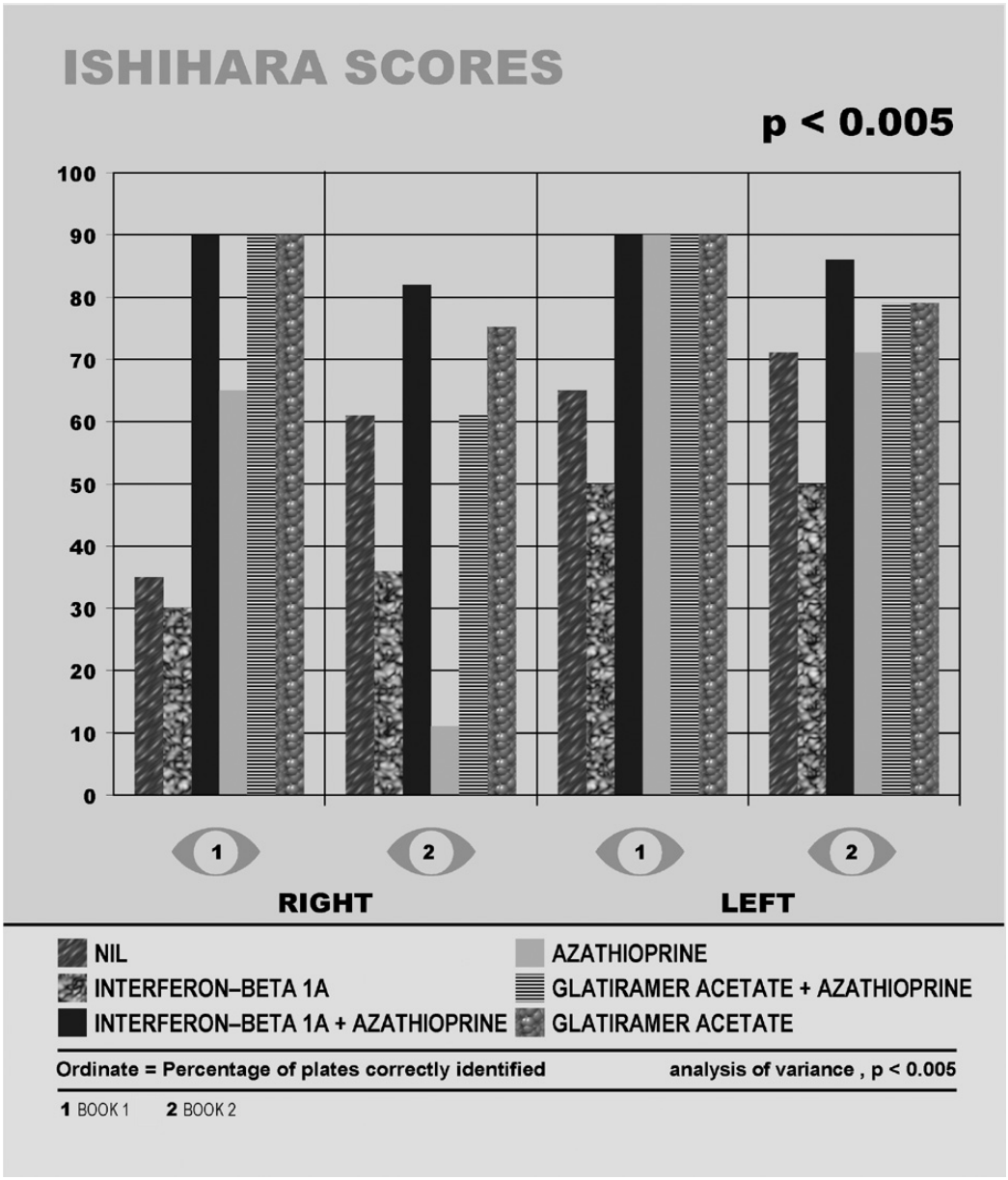

Figure 5.

Discussion of Case 10

The present report describes significant improvements in vision in a patient with progressive optic neuropathy, when Interferon beta-1a or Glatiramer acetate was combined with Azathioprine, but not with any one of these preparations alone.

The evidence is psychophysical: full and half field visual evoked responses, multifocal visual evoked responses, and automated perimetry scores, parameters not necessarily correlated with visual acuity [1, 25], did not alter. Contrast sensitivity scores did not alter reliably with changes in visual acuities.

Nevertheless, the close correlations in visual acuities determined at three distances and Ishihara scores determined with two different books, and an improvement in visual acuities present only when preparations were added, indicates the effect of "combination therapy" is likely to be "real". Confirmation of the changes in visual acuities by a "forced choice" computer generated paradigm, a method considered "robust" and reliable [51], lends strong support to this conclusion. The "reversibility" of the response suggests an effect upon myelin rather than the axon.

The entity might be termed "progressive demyelinating optic neuropathy". It is likely to have been termed previously "idiopathic" optic atrophy or optic nerve "degeneration".

It might be considered a form of "auto-immune' optic neuropathy. Gradual progression, asymmetry of onset in the right and left eyes, lack of "fluctuation" and an absence of vasculitic "markers" differentiates it from other previously described cases [37, 57].

Other causes to be considered but unlikely are chronic relapsing inflammatory optic neuropathy (CRION), not usually steadily progressive, sometimes associated with disc swelling and abnormal MRI signal within the optic nerves; [35] hereditary and mitochondrial optic neuropathies, not known to respond to therapeutic measures; [4, 5] and paraneoplastic effect, unusual in the absence of evidence of neoplasm after 6 years [9].

By analogy with progressive forms of multiple sclerosis, a response to maintenance corticosteroid therapy was considered unlikely. Nevertheless, the possibility remains to be determined.

Therapy is considered likely to have lessened the disparity in times of arrival of impulses transmitted by demyelinated optic nerves, enabling better "processing" within the visual cortices.

Improvement 10 days after the commencement of Azathioprine is unusually premature in neurologic conditions, where, in myasthenia gravis for instance, Azathioprine in combination with steroids has an effect only after months [49]. Yet a comparably early effect of Azathioprine is often evident in renal transplant patients [22].

Neither clinical examination nor evoked response studies are able to distinguish reliably between primarily axonal and primarily demyelinative optic neuropathies. Colour vision loss disproportionate to visual acuity, visual acuity loss disproportionate to optic atrophy, preservation of the nerve fibre layer disproportionate to visual acuity reduction, and a deleterious effect of hot or humid weather suggest, but do not confirm, a primarily demyelinating process. Visual evoked response latencies are not necessarily increased in primarily demyelinating processes.

It is unlikely the effect of "combination" therapy was "indirect", due to a reduction by Azathioprine of neutralising antibody titers. The titer of such antibodies induced by Interferon-beta 1a given by intramuscular injection is low [12]. Antibodies are not considered to impair the action of Glatiramer acetate [66]. Furthermore neutralising antibodies to interferon-beta were undetectable throughout.

In relapsing-remitting multiple sclerosis, interferon-beta and Glatiramer acetate are thought to act by different pathways [8, 11]. That the same effect was found with both Interferon-beta and Glatiramer acetate when added to Azathioprine suggests, in the present case, an action of the two former preparations at the same site, possibly inhibition of the

antigen presenting (dendritic) cell [28]. Azathioprine presumably inhibiting lymphocyte division and antibody production [16].

The therapeutic responses described suggest the need for "pilot" trials of "combination" therapy in other cases of "idiopathic" optic neuropathy and also in progressive forms of multiple sclerosis. If benefit is confirmed, therapy instituted early in the course may lessen "secondary" irreversible axonal loss and lessen or reverse visual decline.

The findings support the likelihood partial and significant reversals of visual and neurological deficits following the addition of low dose Azathioprine to immunomodulatory therapies in some patients with progressive forms of multiple sclerosis described previously [45, 46] reflect a "combination" effect and not the effect of either drug alone. The findings are felt also to support the need to test the hypothesis the rate of decline in the degenerative and some other diseases may be lessened by such "combination" therapy [47].

PATHOGENETIC ASPECTS

Cerebrospinal fluid in multiple sclerosis has long been suspected to be pathogenetic and possibly to account for the predilection of lesions to lie in perivenular, periventricular and surface brain stem sites. Induction of lesions by cerebrospinal fluid from patients with multiple sclerosis in the optic nerves of Xenopus tadpoles, an effect apparently mediated by complement [63], and the high likelihood of definite multiple sclerosis in patients presenting with optic neuritis, having cerebrospinal fluid oligoclonal bands [61], support this possibility. To explore this possibility, techniques used to determine peripheral nerve "excitability" in man [36] might be used in animal preparations to assess the excitability of optic nerves exposed to the cerebrospinal fluid of patients with multiple sclerosis.

Oligoclonal bands are presumed to represent the immunoglobulin secretions of "limited" populations of plasma cells, significantly increased in number in the central nervous system of patients with multiple sclerosis [53]. Should these be pathogenetic, it is possible multiple sclerosis is due to an immune response to a number of, rather than a single, myelin-associated antigens. Should excitability studies of entire cerebrospinal fluid referred to above be helpful, determination of the particular fraction(s) responsible might allow further insights as to the antigen or antigens responsible.

Complement is likely to be particularly important in multiple sclerosis.

As mentioned previously, the C3d component of complement appears to play a role in microgliocyte activation in progressive disease. The binding of C3d to laminin within the placenta [39]may account, in part, for the diminished relapse rate in the later stages of pregnancy [13].

Complement is able to induce apoptosis [27]. Oligodendrocyte apoptosis may be the initial event in the evolving acute lesion [2]. Immunoglobulin and the membrane attack complex (MAC) of complement are present in areas of acute demyelination [56]. Intravenous gamma globulin is thought to act, at least in part, by reducing activity of the membrane attack complex (MAC) of complement [3]. It is of interest, therefore, a reduction in disability scores and no relapses were observed in the three years thirty four patients with relapsing-remitting disease were administered Azathioprine and intravenous gamma globulin [33].

These observations suggest a pathogenetic role of complement in relapsing-remitting disease, possibly activated by cerebrospinal fluid immunoglobulins. Were disease progression to be rapid or severe, cerebrospinal fluid pheresis, reported to be beneficial in cerebral lupus erythematosus [50], in combination with immunomodulatory, immunosuppressive and steroidal therapies might be contemplated.

Pathologic studies in secondary progressive multiple sclerosis, referred to in the previous section, suggest "periplaque" demyelination contributes to disease progression. Progressive deficit in multiple sclerosis thus may be due to a "leading edge" of demyelination with, in its "wake", secondary, gradual and progressive axonal loss.

That axonal loss in progressive multiple sclerosis, as evidenced by magnetic resonance spectroscopy [44], is secondary to myelin loss is suggested by the following: animals with genetically determined myelin deficiencies suffer secondary axonal loss [6]. Intravenous methylprednisolone infusions in long standing progressive multiple sclerosis often lead to transient improvements, particularly strength. The superior cerebellar vermis in long standing progressive cases with ataxia, imaged by magnetic resonance image scans, may be normal.

Possibly the most common clinical manifestation of "minimal" progressive disease is a midline cerebellar deficit, characterised particularly by failure to suppress visually the vestibulo-ocular reflex and difficulty in the execution of tandem gait. Visual suppression of the vestibulo-ocular reflex in animals reflects the integrity of the flocculus [30, 64]. Perhaps then, the myelin of the cerebellar flocculus might be analysed to determine if its structure differs from myelin elsewhere in the central nervous system.

It seems likely relapsing-remitting disease returning to baseline and progressive disease represent separate immunologic entities, a postulate likely to appeal to the attending clinician. Perhaps, the alteration of sufficient quantities of the antigen(s), giving rise to the usually more severe and, at times, axonally destructive "relapse lesion" , results in the presentation of a new antigen in disrupted myelin, resulting in the usually more gradual, primarily demyelinating, secondary progressive form. The genetic constitution of those suffering primary progressive forms may "ab initio" present the "altered" antigen of secondary progressive disease to the immune system.

The finding of a serologic "marker" of neuromyelitis optica (Devic's disease) [72], an entity in which microscopic findings resemble closely multiple sclerosis, suggests more exact, possibly serologic and genetic, classifications in the future.

It is entirely possible, although not observed in the present series, that should the therapeutic effect of combination therapy reflect a beneficial effect upon myelin, restoration of the integrity of myelin will, after a time, lead in relapsing-remitting cases to a representation of the initial antigen(s) and a further cascade of relapse and remission. Should such "secondary" relapses be observed in an identical twin pair, where disease expression is not concordant [15], "comparative" serologic studies might determine the nature of an agent, predisposing to relapse in the affected member.

NOSOLOGIC ASPECTS

The point of transformation of relapsing-remitting to secondary progressive disease has been considered to be indistinct and able to be made only in retrospect.

Compensation for cerebellar deficit due to a single self-limiting event, such as infarction or haemorrhage, is usually complete after one to two months.

Persistent cerebellar signs, usually "midline", therefore, are most likely to indicate underlying disease activity, rather than a previously sustained and no longer active cerebellar insult. Yet such signs are commonly present in relapsing-remitting patients in "remission". Furthermore, the current concept of relapsing-remitting disease does not distinguish between patients returning to apparent "normality" between relapses and those whose deficits increase in "step wise" fashion.

It might be argued a distinction should be made between these groups. Patients who return to normal or near normal between relapses without cerebellar signs might be considered to suffer relapsing-remitting disease. Those with stable deficits and cerebellar signs might be considered to suffer progressive disease, in which injurious and reparative forces are "in balance". Patients currently considered to be relapsing-remitting with increasing step-wise deficit and patients currently considered progressive might be considered "progressive", the strength of injurious forces exceeding reparative forces.

The tenth case, labelled prior to combination therapy, "idiopathic" optic atrophy, must, in view of marked improvement with therapy, be a demyelinating optic neuropathy. A marked improvement in vision following combination therapy suggests a similar demyelinating process to multiple sclerosis. Indeed, it might be argued, the case represents a form of "monosymptomatic" multiple sclerosis, a description not in keeping with current convention. Semantics aside, the importance of the case is that it suggests that some patients with monosymptomatic deficits, for instance "idiopathic optic atrophy" or "transverse myelitis", may respond to combination therapy, preferably instituted early in the course.

RELEVANCE TO THE DEGENERATIVE DISEASES

Abstract

The hypothesis a pathway common to the degenerative diseases, amenable to particular therapies, is discussed. C3d, formed by activation of the complement cascade, amplifies markedly the synthesis of immunoglobulin, that may increase microglial activation and thus induce neuronal damage and death. If indeed the formation of C3d and activated microgliocytes are critical steps in the degenerative pathway, "combination therapy" utilising immunomodulatory and immunosuppressive preparations, the former to inhibit the antigen presenting (dendritic) cell and the latter to inhibit lymphocyte activation, may ameliorate the degenerative process.

Introduction

Genetic, environmental and immunologic mechanisms are thought to contribute to the degenerative diseases. Purely genetic processes do not explain an usually inexorable progression and predilection for certain sites. Moreover, definite genetic contributions are usually not discernible in the common degenerative diseases. An environmental factor might be expected to result in a "discrete' deficit, that does not progress, or regresses, when the contributory factor is no longer present.

Activated microglia in areas of neuronal loss are usually found in the degenerative diseases. Such "activated" microglia are able to elaborate factors, that upregulate the genetic transcription of abnormal proteins and deleterious cytokines, impose oxidative stress and induce apoptosis [10, 50]. Neuronal damage induced by genetic, environmental or immune processes may present to the extracellular environment and hence to immunologic surveillance mechanisms "disrupted" or altered cellular components.

In addition to possible "primary" deleterious effects, such components, either of themselves or by inducing immunoglobulin synthesis, may activate the complement cascade, resulting in the formation of the complement component, C3d. C3d binds covalently to the CD21 (CR2) receptor. By co-ligating the CD21 receptor of B lymphocytes to proteins, C3d greatly amplifies immunoglobulin synthesis by a transduction signal, that activates the CD21/CD19/CD81 cascade [19]. For instance, the attachment of three molecules of C3d to hen egg lysozyme reduces the threshold immunising dose by a factor of 10,000 [14]. Immunoglobulin synthesised by lymphocytes and plasma cells activates microgliocytes by binding to the Fc receptor.

That microglia activated by Fc receptors contribute to disease progression is suggested by the following: immunoglobulin from patients with Parkinson's disease damages dopaminergic cells in culture [38], and when injected into rat substantia nigra, depletes cells in the pars compacta [26], both effects requiring the microglial Fc gamma receptor; immunoglobulin from patients with motor neuron disease increases calcium and neurotransmitter release from motor neurons in mice, an effect mediated by the microglial Fc gamma receptor [48].

C3d is widely present in the degenerative diseases. It is present, for instance, in the neuritic plaques of Alzheimer's disease, the Lewy bodies of Parkinson's disease, in morphologically intact neurons of motor neuron disease, within the spongiform neuropil of prion disease in "plaque-like" forms, amidst the melanin granules of retinitis pigmentosa, and within the hard and soft exudates of macular degeneration [42, 73, 21].

The variable and usually inexorable "progression" of progressive multiple sclerosis mimics that of the degenerations. Disrupted myelin invested by C3d and activated microgliocytes at the edge of long standing plaques were suggested by Prineas et al to contribute to disease progression in progressive multiple sclerosis [56]. In an open label study, immunodulatory therapies (one of the three forms of Interferon beta-1b or Glatiramer actetate) and Azathioprine in combination were found, in a proportion of patients with progressive forms of multiple sclerosis, to reverse partially visual and neurologic deficits [45, 46].

The effects of such "combination therapy", not present following the administration of either drug alone, might reasonably be the result of actions at separate sites, immunomodulatory therapies possibly inhibiting the antigen presenting (dendritic) cell [28]and Azathioprine lymphocyte activation and hence immunoglobulin synthesis. Quantitative MRI studies in relapsing-remitting multiple sclerosis patients receiving such combination therapy [43] lend support to these observations, that require confirmation by controlled trials.

Hypothesis

If such effects are confirmed and reflect inhibition of C3d synthesis and microglial activation, "combination therapy" may lessen the rate of decline in the degenerative diseases, to which the term "the C3d-microgliocytoses" might be applied. The degree of benefit might vary inversely with the immunogenicity of the antigen. For instance, the intense microgliocytosis of prion disease suggests an immunogenicity so greatly increased, as possibly to preclude a therapeutic response. Perhaps physiologically related systems are antigenically related, a speculation relevant to affection of upper and lower motor neuron elements in motor neuron disease.

"Reversals" in multiple sclerosis, presumably due to a beneficial and possibly regenerative effect upon myelin, would not be expected in the degenerations,in which neurons are unable to regenerate. Progression in diseases outside the brain, for instance; glaucoma, in which apoptosis may be a contributory process; cardiomyopathy, in which complement may play a part; [34] and type I diabetes, in which lymphocytic infiltration may not be apparent [23], may also share a similar pathway, possibly amenable to similar therapy.

Testing the Hypothesis

Motor neuron disease and Alzheimer's disease are examples in which current methodologies are able to determine, in transgenic animal models and human subjects, in short time spans, a possible therapeutic effect. The possibility of further improvement with the addition of intravenous gamma globulin, able to inhibit the third arm of the pathway, activation of the microglial Fc receptor [3], might also be determined.

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