Neurodegeneration and multiple sclerosis

Axel Petzold

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Abstract

Neurodegeneration causes inexorable loss of neurons and function in both diseases and aging. Neurodegeneration damage produces a range of progressive disabilities from cognitive decline, behavioral, and mood disorders to problems with movement, coordination, and sensory dysfunction. Neurodegeneration is a major and growing public health issue which in its broadest sense embraces classical neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, as well as multiple sclerosis (MS), diabetes, acute brain injury among many other conditions. This chapter discusses the clinical and pathophysiological features of neurodegeneration in MS.

Keywords: Demyelinating disease, Multiple sclerosis, Neurodegeneration, Trans-synaptic axonal degeneration, Protein biomarker, Cerebrospinal fluid, Retina, Optical coherence tomography

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1 Introduction

Neurodegeneration causes inexorable loss of neurons and function in both diseases and aging [126]. Neurodegeneration damage produces a range of progressive disabilities from cognitive decline, behavioral and mood disorders to problems with movement, co-ordination, and sensory dysfunction. Neurodegeneration is a major and growing public health issue which in its broadest sense embraces classical neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, as well as multiple sclerosis (MS), diabetes, acute brain injury among many other conditions. This chapter discusses the clinical and pathophysiological features of neurodegeneration in MS.

The historical context will be discussed first, because our understanding of MS pathology has been much influenced by demyelination and a concept of dissemination in time and space [32, 80]. Next, the classical pathological features of neurodegeneration in MS are reviewed in more detail [90]. Axonal loss will be placed centrally because of the important link to irreversible loss of function [90, 103, 126]. The resulting disability has a major impact on an individual patient's life [103]. Here limitations will be reviewed of those clinical and paraclinical assessments which were predominantly focused on demyelination and/or evidence for dissemination in time and space [32, 79]. It is against this backdrop that biomarkers for neurodegeneration will be presented [22]. The chapter closes with an outlook on how this knowledge may be applied to future treatment trials targeted at halting neurodegeneration in MS [103].

2 Historical Context

Most of the credited clinico-pathological descriptions of MS date back to the mid nineteenth century. The classical pathological features embrace inflammation, demyelination and gliosis [90, 95, 126].

Jean Marin Charcot, who pioneered the pathophysiological explanation of the symptoms observed in patients distinguished three steps in the pathology of MS, which he called *la sclérose en plaques disseminée, la sclerose generalisée et la sclerose multiloculaire*. First, astrocytic and microglial activation: *"la multiplication des noyaux et l'hypertroplasie concomitante des fibres réticulées de la névroglie sont le fait initial"*. Sec-

ond, neuro-axonal degeneration: *"l'atrophie dégénerative des éléments nerveux est secondaire"*. The interested reader is referred to a wonderful historical account on axonal pathology for more details [66]. And third, astrogliosis: *"la névroglie fait place au tissu fibrillaire"*. Ultimately, it was demyelination ("dépouillés de leur myéline" [21]) which became the key pathological feature of the disease, here depicted in a frequently cited sketch (Figure 1).

The cause for these features has remained enigmatic ever since James Dawson's dichotomization into "inflammatory" and "developmental" concepts [25] [1].

Whilst pathologically succinct, the difficulty for the treating physician remains to recognize and communicate a diagnosis of MS to the patient. Historically, MS was recognised in the pre-antibiotic area where inflammatory diseases such as syphilis presented major public health issues. Separating one from the other was not always straightforward. Not surprisingly, given the multitude of symptoms and signs mimicking other diseases, MS was also considered a chameleon. In absence of a diagnostic test the clinical judgement cannot be substituted for. This notion is reflected in a series of diagnostic criteria, all more or less stating that the patient's symptoms and signs ought to be compatible with the characteristics of MS [96, 113, 115]. The careful and systematic, evidence-based approach on which these criteria rest, distilled a conceptual framework which may be phrased as "dissemination in time and space" [32].

Dissemination in time (DIT) and dissemination in space (DIS) are well suited to describe the occurrence of radiologically recognizable MS lesions in the brain and spinal cord [32].

It was precisely the absence of clear evidence for these characteristic features which made it so challenging to develop diagnostic criteria for primary progressive multiple sclerosis (PPMS) [138]. Later, Thompson and colleagues phrased this as: "Neither set of criteria is appropriate to PPMS, since the basic requirement of two discrete episodes of neurological dysfunction cannot by definition be fulfilled." [136]. The clinical corner stone of what emerged in International Panel diagnostic criteria was the documented clinical progression for more than one year [113].

Paradoxically, the first *in vivo* observation of axonal loss in MS was diffi-

[1] This dichotomisation remains a persistent intellectual concept with changing names such as "exogenous versus endogenous", "outside-in versus inside-out".

Figure 1: The figure shows the original sketch of an MS lesion from the landmark paper of Charcot [21]. The image depicts a fresh MS plaque colored with carmine. Charcot's text implies presence of axonal pathology based on morphological observations of diameter and continuity. His interpretation is careful as he does not exclude possible preparation- related artifacts. The original text reads as: "Elle représente une préparation frâche, provenant du centre d'une plaque scléreuse, colorié par le carmin et traité e par delacération. Au centre, vaisseau capillaire portant plusieurs noyaux. A droite et à gauche, cylindres d'axe, les uns volumineux, les autres d'un très–petit diamètre, tous dé pouillés de leur myéline. Le vaisseau capillaire et les cylindres d'axe étaient fortement colorés par le carmin. Les cylindres d'axe ont des bords parfaitement lisses, ne presentant aucune ramification. Dans l'intervalle des cylindres d'axe, membranes fibrilles de formation récente, à peu près parallèles les unes aux autres dans la partie droite de la préparation, formant à gauche et au centre, une sorte de réseau résultant, soit de l'enchevêment, soit de l'anastomose des fibrilles. Celles–ci se distinguent des cylindres d'axe, 1 par leur diamètre qui est beaucoup moindre; 2 par les ramifications qu'elles offrent dans leur trajet; 3 parce qu'elles ne se colorent pas par le carmin. — C á et et là , noyaux disséminés. Quelques–uns paraissant en connexion avec les fibrilles conjonctives; d'autres ayant pris une forme irre gulière, due à l'action de la solution ammoniacale du carmin."[21].

cult to publish at all, according to anecdotal reports from the authors. Hoyt and colleagues had observed retinal nerve-fiber bundle defects in the eyes of patients with MS [50]. Much more frequently cited is the follow-up paper on this observation by Frisen *et al.* stating the presence of "insidious atrophy" of retinal nerve fibers in the eyes of patients with multiple sclerosis [36]. The second case reported by Frisen and Hoyt was a 15-year old student athlete with a clinical diagnosis of "multifocal demyelinating disease," but without any history of optic neuritis. One may speculate that one argument for rejection at the time might have been that multiple sclerosis was a demyelinating disease and the question was raised: why should there be at all atrophy of the non-myelinated axons in the eye of a patient who did not even suffer from optic neuritis?

Axonal loss was only some 24-years later firmly put on the MS research agenda by the American cell biologist Bruce Trapp and the Norwegian pathologist Lars Bo [140]. The conceptional change this influential pathological study had will be discussed in the next section.

3 Pathological Features

3.1 Axonal Loss in Multiple Sclerosis

In order to put the observation by Trapp *et al* into context, one needs to recall that axonal pathology may not be the most striking feature in the MS brain, but certainly is the one with the highest impact for the patient [94, 139, 140, 148, 151]. Historically, axonal loss in MS has been been associated with the "burnt-out" phase of the disease [41, 118]. Only with the wide availability of immunohistological techniques it was possible to demonstrate axonal pathology in *active* MS lesions [31]. There was extensive staining for amyloid precursor protein (APP) and the APP positive structures resembled transected axons. It was however the, three dimensional reconstruction of these axonal ovoids, using confocal microscopy, which conclusively demonstrated axonal transections within acute MS lesions [140]. Interestingly, an accumulation of neurofilament protein was observed in the so-called "end-bulbs." In vivo imaging of the development of axonal degeneration is available for experimental models [62, 93, 97].

In other words, the important new insight from this work was that a high number of transected axons were already present in acute lesions [31,

140] and in patients with a short clinical course [140]. This data changed the earlier perception of axonal loss in MS [20, 121].

The data from Trapp *et al.* is consistent with the concept that an important trigger for axonal loss are MS lesions [80]. But because disability continued to progress even after successful suppression of the inflammatory part of the disease, other aspects of axonal pathology were discussed [132]. Axons might be driven into a fatal energy deficit [90, 134, 141]. There is good evidence that mitochondrial pathology and sodium channel redistribution contribute to an "ATP penalty" [14, 19, 49, 81, 91, 150]. Axonal transport might be impaired [11, 67, 106, 127]. Next, there might be loss of trophic support or increase of inhibitory substances such as Nogo [52]. A barrier may result from astrogliosis. A low-grade inflammatory process might persist [48]. There is the problem of failure to remyelinate. There may be acceleration of physiological processes of aging-related neurodegeneration. Endogenous capacities of repair might have their limits [48]. In sum, those factors causing axonal degeneration might eventually outnumber those which were protective [130].

It is worthwhile to remember some limitations, axonal injury remains a dynamic process and quantification of axonal loss in histological material might be complicated by tissue edema, the presence of inflammatory cells and the problem of establishing a relationship with the number of healthy axons. There is a crucial dependence on well-preserved tissue with limited capacities of the existing brain banks. Most post-mortem studies were biased to tissue from patients with long-standing disease duration and there is a lack of representative tissue from the clinically and therapeutically relevant early disease phase. Some early tissue might be available through biopsy, but again questions might be asked how representative such tissue really is if taken because the presentation was very atypical. Finally, there are shortcomings to the analytical methods, dyes, and antibodies used.

3.2 Concepts of Axonal Degeneration

Like axonal injury, axonal degeneration is also a dynamic process. Most recent insights come from experimental studies in mice on flurorescently labeled axons [62, 122]. It may be opportune to go back in time and re-visit the first systematic description of axonal injury by Waller which gave rise to the eponym "Wallerian degeneration" [143].

In brief, Wallerian degeneration is a complex process which describes the degeneration of the *distal* axonal stump after axonal transection from the neuron. Wallerian degeneration begins with the enzymatic proteolysis of the axonal cytoskeleton [40]. Additionally, Wallerian degeneration affects also the sheathing glial cells, causes alterations in the adjacent blood-tissue barriers, and stimulates cells of macrophage lineage. From a mechanistic point of view Wallerian degeneration is of anterograde direction.

Wallerian degeneration has to be distinguished from *dying back* neuropathy, defined as the slow *proximal* spread of nerve fiber breakdown and ultimate apoptosis of the neuron [131]. The term *dying back* was introduced to describe the spatio-temporal pattern of central and peripheral nerve fiber pathology in degenerative diseases. Contemporary understanding is that axonal degeneration is defined by direction into anterograde and retrograde .

An important, mechanistic question to be asked is how the process of neurodegeneration can spread from a sick to a healthy neuron/axon? One attractive concept is *trans-synpatic* axonal degeneration [56, 58]. These authors used a non-invasive, utrarapid imaging technique, readily tolerated by patients, retinal optical coherence tomography (OCT) [57]. The study design was elegant and simple by focusing on neurodegeneration in the visual pathways. Following a stroke in the posterior visual pathways, dying-back neuropathy spread (trans-synaptic) from the second order neuron located in the lateral geniculate nucleus (LGN) to the axons (retinal nerve fiber layer, RNFL) of the first order neuron (retinal ganglion cell, RGC) [56, 58]. These studies have advanced the understanding of acquired axonal degeneration [26].

In addition to retrograde transynaptic axonal degeneration, there is evidence for anterograde trans-synaptic axonal degeneration from a post-mortem study of the visual system of patients with multiple sclerosis [29].

Taken together, these data suggests a concept of *bi-directional (trans-synaptic) axonal degeneration* [7] (Figure 2).

The attraction of this unified concept of bi-directional (transynaptic) axonal degeneration is that not only it is convenient to explaining how neurodegeneration spreads in MS, but more importantly it may contribute to opening a therapeutic window for future neuroprotective strategies in MS. The aim here will be to prevent the trans-synaptic part of the degenerative process and thereby at least limit the impairment for the patient.

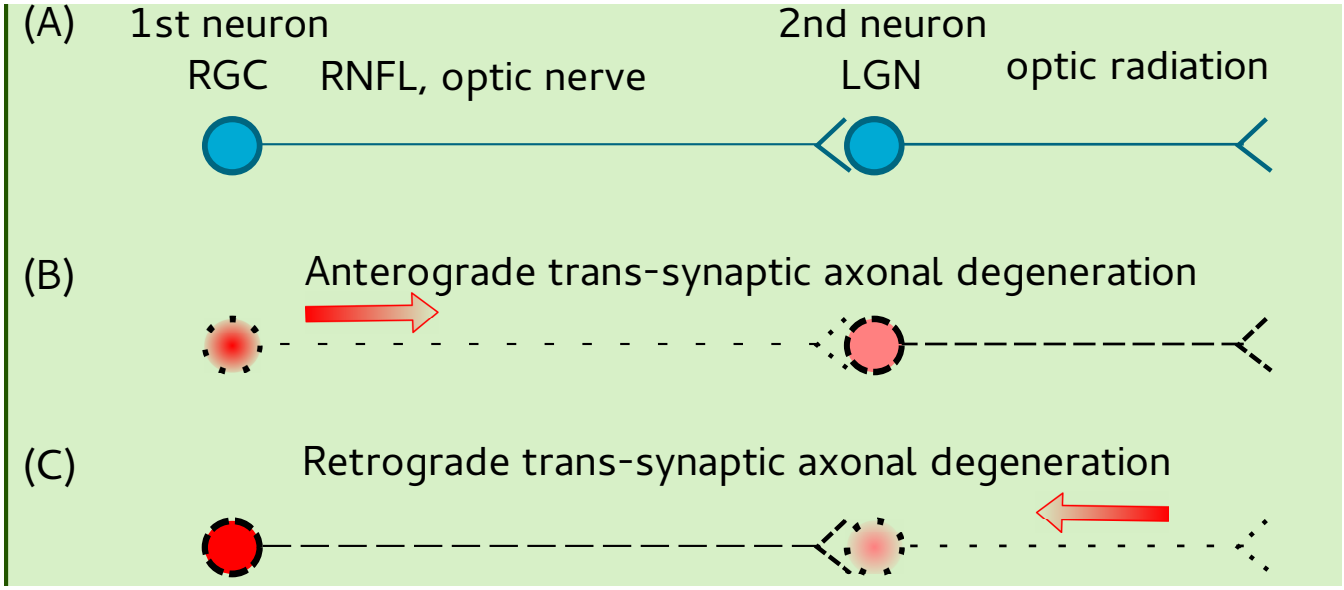

Figure 2: *A simplified and uniform mechanistic concept of axonal degeneration.* ***(A)*** *The normal situation is here shown for the visual system. The first order neuron is represented by the retinal ganglion cell (RGC). The first axon is represented by the retinal nerve fiber layer (RNFL) which is named optic nerve after the axons passed through the lamina cribrosa. Here an axon is shown to synapse in the lateral geniculate nucleus (LGN) with the second order neuron. Next, the second neuron sends its axon through the optic radiations to the occipital cortex.* ***(B)*** *Anterograde axonal degeneration starts at the RGC/RNFL/optic nerve (e.g. with optic neuritis). Once anterograde axonal degeneration reaches the LGN, it continues as trans-synaptic anterograde axonal degeneration.* ***(C)*** *Retrograde axonal degeneration starts with axonal transections in the optic radiations (e.g. with eloquently placed white matter lesions). Once retrograde axonal degeneration reaches the LGN, the process continues as trans-synaptic retrograde axonal degeneration. Ultimately this leads to loss of retinal nerve fibers and apoptosis of the RGC. Longitudinally, the transynaptic part of this concept of bi-directional axonal degeneration will always have to occur with a time-lag. Understanding this timelag may potentially open a new therapeutic window for future neuroprotective strategies in MS*

4 The Patient

The use and definition of terms to describe a patients impairment, disability and handicap in this section were based on the recommendations of the system adopted by the World Health Organization (WHO).

Impairment describes the "loss or abnormality. . . of structure of function. *Disability* describes "a restriction or lack. . . of ability to perform an activity in the manner of within the range considered normal for a human being". *Handicap* describes "the disadvantage for an individual. . . that prevents or limits the performance of a role that is normal. . . for that individual". To be more specific, handicap represents the effects of impairments or disabilities in a wide social context and may be substantially influenced by the cultural background.

By definition (DIS and DIT [32]), a patient will suffer from MS related symptoms causing potentially reversible impairment in different parts of his/her body. From a patient's perception, gait and vision are the two most valuable functions [47]. Both gait and vision topped a list of 13 bodily functions during the early ($<$ 5 years) and late ($>$ 15 years) disease course. Importantly, early in the disease were patients were still ambulatory, gait was rated more valuable compared to visual function, but there was a crossover with long-disease duration. With the ever increasing use of visual communication channels (e.g., smart phones, tablets, social media), it can be anticipated that from a patients point of view the value and dependence on the visual system will continue to increase in the near future. This may be particularly true for those handicapped patients who crucially depend on the visual system for social interaction. Not surprisingly all of above is related to a patients Quality of Live [8].

Two questions are frequently asked by patients: "Will this happen again?" (relapse and "Will I end up in a wheel-chair?" (neurodegeneration). The first one may, with caution, be answered based on the momentary clinical and radiological disease activity. Addressing the second question is more challenging because of a relative lack of longitudinal data from well-validated outcome measures for neurodegeneration.

5 Clinical and Paraclinical Assessments

> "There are few neurological diseases in which the diagnosis depends so much upon the skill of the examiner in knowing what questions to ask and how to interpret the replies." [114]

5.1 Clinical Scales

Impairment or loss of function is quantified by clinical scales. The paradox between clinical examination and each clinical scale is that normal functioning is tested, but loss of function is quantified. Because of the potential of CNS regeneration and plasticity, the clinical appearance of disability is a dynamic process. This forms the basis on which MS patients had been classified [86]. A more recent approach separated an "active" from a "non–acitve" subtype based on clinical and MRI data [87].

A range of validated clinical scales is now in use. For MS the most widely applied scale is the extended disability status scale (EDSS) for multiple sclerosis developed by Kurtzke in 1983 [78]. The EDSS combines a disability status scale [76] with functional systems [77]. For a comprehensive up to date review of outcome measures in MS the reader is referred to van Munster and Uitdehaag [99].

Psychometry is tested by the Paced Auditory Serial Addition Test (PASAT) [42]. The National Adult Reading Test (NART) is used to give an estimate of the premorbid IQ [101]. Current intellectual function is assessed by the Advance Progressive Matrices, Set 1 (Ravens). Memory is assessed by recognition of words and faces [144]. The paired associated learning test estimates learning abilities. Attention is readily quantified by the speed of letter counting [149]. Tests of executive function include the Wisconsin Card Sorting Test (Nelson) and the Cambridge Neuropsychological Test Automated Battery (CANTAB) [101, 125]. Fatigue is commonly estimated by Krupp's Fatigue Rating Scale [68]. Anxiety and depression have been measured using the National Hospital anxiety and depression scale (HAD) measuring quality of life and measures for outcome of neuro-rehabilitation [137].

The timed walk test (TWT), 9 hole peg test (9HPT) and Paced Auditory Serial Addition Test (PASAT) have been combined mathematically to give the Multiple Sclerosis Functional Composite (MSFC) [24, 99]. The MSFC

has the potential to provide a more reliable measure of changes of function in MS than the EDSS, which is non-linear and biased toward locomotion [9]. In addition, the MSFC may be perceived as a “melting pot” which permits to embrace other relevant clinical measures within a statistically valid concept. One potential extension of the MSFC may be low contrast letter acuity [6]. One advantage of such multidemensional measures relates to the potential to cover both disease activity and progression in MS [99].

A cross-sectional measure of disease severity in individual patients is provided by the global Multiple Sclerosis Severity Score (MSSS) [124]. The global MSSS is taken from a statistically constructed “look-up table.” This table provides normally distributed disease severity scores for patients with an EDSS between 0 and 9.5 and a disease duration between 1 to 30 years.

Newer developments include patient-reported outcome measures (POM) [99]. A well established example for a POM is the MSIS-29 [46].

The advantages of clinical scales (and questionnaires) are that they may provide a more holistic view of an individual patients disability compared to paraclinical tests. But there are also limitations to be considered:

1. Psycho-physiological testing heavily depends on the patient’s cooperation and motivation.

2. Biased to data from the system tested. This has been a frequently discussed limitation of the EDSS which is biased to the pyramidal system.

3. Learning effects. This is particularly challenging for testing cognition longitudinally.

4. Challenges of validation across cultural and language-barriers. This may impact on the use as an outcome measure in multi-center studies.

5. Multiple biological causes for poor performance. In MS this includes:

   (a) Conduction block

   (b) Demyelination

   (c) Axonal loss

5.2 Paraclinical Tests

> "The technological advances that have contributed to a better understanding of the pathophysiology and pathogenesis of MS have resulted in a disturbing increase in the number of false diagnoses of MS based exclusively on the results of test procedures." [114]

Paraclinical tests are a double-edged sword, but do have their merits in experienced hands if used as an extension of the clinical reasoning. The four most frequently used paraclinical tests over the past 50-years comprise in alphabetical order: cerebrospinal fluid (CSF), computed tomography (CT), MRI and visual evoked potentials (VEP), acknowledging that MRI has become the sole paraclinical test of the 2010 revision of the McDonald criteria for RRMS [113]. A historical head-to-head comparison based on the earlier Poser criteria is presented in Table 1.

Of note, none of these studies investigated the relevance of any of these tests for axonal loss, which as pointed out earlier was not the main focus of MS research at the time.

Table 1: *Paraclinical tests used in MS. For each test the diagnostic sensitivity of the respective study is presented alongside the author's main conclusions.*

Reference	Test	Sensitivity	Conclusion
Polman *et al.* [112]	CSF	72.2%	diagnostic classification
	CT[2]	17.0%	differential diagnosis
	VEP	62.0%	diagnostic classification
Beer *et al* [10]	CSF	77%	best re-classification specificity
	MRI	84%	highly sensitive, demonstrates DIS
	VEP	37%	useful if MRI and CSF are not diagnostic
Filippini *et al* [33]	CSF		
	MRI	70%	most sensitive test
	VEP		

While sensitive for diagnostic purposes, the limitations of MRI to *predict* development disability were elegantly summarized by Kappos and col-

[2]This study also included a very small, n=3, number of MRI scans, BAER and SSER.

leagues in a thoroughly conducted meta-analysis: “Neither the initial scan nor monthly scans over six months were predictive of change in the EDSS in the subsequent 12 months or 24 months. The mean of gadolinium-enhancing-lesion counts in the first six monthly scans was weakly predictive of EDSS change after 1 year (odds ratio=1.34, p=0.082) and 2 years (odds ratio=1.65, p=0.049)” [60].

This meta-analysis demonstrates the difficulties in predicting accumulation of irreversible disability, which is related to neurodegeneration, based on a paraclinical test focused on inflammatory disease activity. In contrast, MRI data on CNS atrophy are much better correlated to sustained disability [16, 35]. There is data on perfusion, functional MRI, high-field MRI, new sequences specifically addressing iron storage, double inversion recovery (DIR), and MR spectroscopy (MRS). For in-depth review of these and other MRI techniques the reader is referred to recent reviews on the issue [39, 61, 123, 145].

Likewise, for the CSF there is conflicting evidence on the relationship of CSF oligoclonal bands (OCBs) and disability [108]. There are some reports suggesting that the absence of OCBs in the CSF of patient with MS may be a good prognostic sign [30, 59, 69, 82, 98, 153]. Others did not find any prognostic value of either presence or absence of CSF OCBs [51, 65, 84].

There may also be leverage using VEPs (and other evoked potentials) as a paraclinical test for neurodegeneration in MS [79].

It may be suggested to separate those paraclinical tests which permit detection of axonal loss (and neurodegeneration) in the acute phase from those which are superior for documenting axon loss after some time has elapsed. Tentatively, retinal OCT was added to this list as an emerging paraclinical test for retinal layer atrophy:

1. Early phase of ensuing axonal injury and loss:
    - Biomarkers for acute axonal damage [27, 109, 133]
    - Imaging markers for neuronal dysfunction and apoptosis [23, 100, 146]
2. Late phase of axonal loss having resulted in manifest atrophy:
    - MRI atrophy markers [83, 147]
    - OCT [18, 110]

- VEP and motor evoked potentials (MEP) [64, 79]

5.3 Acute Neurodegeneration in MS: Body Fluid Biomarkers

In MS disintegration of the axonal membrane causes release of biomarkers from injured axons and neurons in the surrounding extracellular fluid (ECF) [104]. These biomarkers diffuse from the brain ECF into the CSF and blood. Sampling from each of these body fluid compartments is possible with related advantages and disadvantages.

A review of the biomarker literature in MS shows that most early studies were cross-sectional and frequently of limited sample size [4, 12, 13, 28, 71, 109]. This radically changed in the past two years. Pioneering studies relied on in–house developed immunoassays for the quantification of biomarkers. With availability of commercial tests for quantification of key biomarkers such as the neurofilament proteins from the blood the literature on the subject as increased exponentially [5, 27, 38].

Because of the essentially correlative nature of clinical biomarker investigations, only a snapshot in time is provided by cross-sectional studies. Not surprisingly, some studies find a clinical relevant correlation for a particular biomarker, while others do not. Some of these issues can be addressed by a meta-analysis. It will however be much more important to obtain high quality long-term data. Therefore, Table 2 summarizes blood biomarkers categorized to their cell-type-specificity. For an extended biomarker table and in-depth review on CSF biomarkers for Neurodegeneration see [28, 102, 104].

Table 2: *Blood biomarkers in MS and their cellular sources.*

Blood Biomarker	Neuron and Axon	Astro-cyte	Micro-glia	Oligoden-drocyte	Other cells
14-3-3γ	+	+	+	+	+
Amyloid β42	+				
Apo-E	+	+	+		
FABPs	+	+	+	+	+
FFA	+	+	+	+	+
Ferritin			+		+
GAP-43	+				
Gelsolin	+				+
GFAP		+			

HNE	+	+	+	+	+
NSE	+				+
Neurofilaments	+				
S100B		+		+	+
Tau	+	+	+	+	+
UCHL-1	+				

The measurement of cell-type specific biomarkers indirectly permits to estimate the degree of damage to the respective cellular source. For example, an increase of blood neurofilament (Nf) levels gives indirect evidence for neuro-axonal damage. Neurofilaments have consistently found to be of prognostic value in MS [3, 17, 27, 44, 70, 74, 75, 88, 89, 92, 107, 111, 135].

Importantly, there has been convincing analytical and experimental work to substantiate the hypothesis that Nf levels are related to neurodegeneration [1, 5, 45, 53, 54, 72, 85, 105, 116, 128, 135]. Tests are now commercially available with the most sensitive technology being Simoa [73].

5.4 New Validated Atrophy Related Imaging Biomarkers for Neurodegeneration: Optical Coherence Tomography

An emerging imaging technology for neurodegeneration in MS is retinal optical coherence tomography (OCT) [110]. The results of the early time-domain OCT meta-analysis have now been repeated for spectral-domain OCT. The results of the two meta–analyses were almost identical underlining the robustness of the method.

While it is well known that optic neuritis causes loss of the retinal nerve fiber layer [36], it only recently emerged that such atrophy can also be present in eyes not affected by optic neuritis [2, 15, 34, 37, 43, 55, 63, 110, 117, 119, 120, 129, 142, 152]. Because retinal nerve fiber layer (RNFL) thickness also correlated with clinical scales and MRI measures there is a need to test the reliability and validity of OCT in a multi-center setting.

6 Outlook

Taken together, neurodegeneration is an important feature of MS pathology because it is responsible for irreversible disability in patients. The dynamic nature of neurodegeneration poses challenges to the techniques used for monitoring. Some methods have their strengths in the acute phase; others only become reliable once neurodegeneration becomes manifest as atrophy. A holistic model combining the respective strength and weaknesses is presented in Figure 3.

This may be an opportune moment to end this chapter with an open question building on an analogy. In diabetes mellitus patients measure several times per day their blood glucose levels to optimise individual treatment. Additional paraclinical tests are used to closely monitor related organ damage with the aim to further guide patient management. How can we combine our respective expertise and methods to achieve a similar feat in MS?

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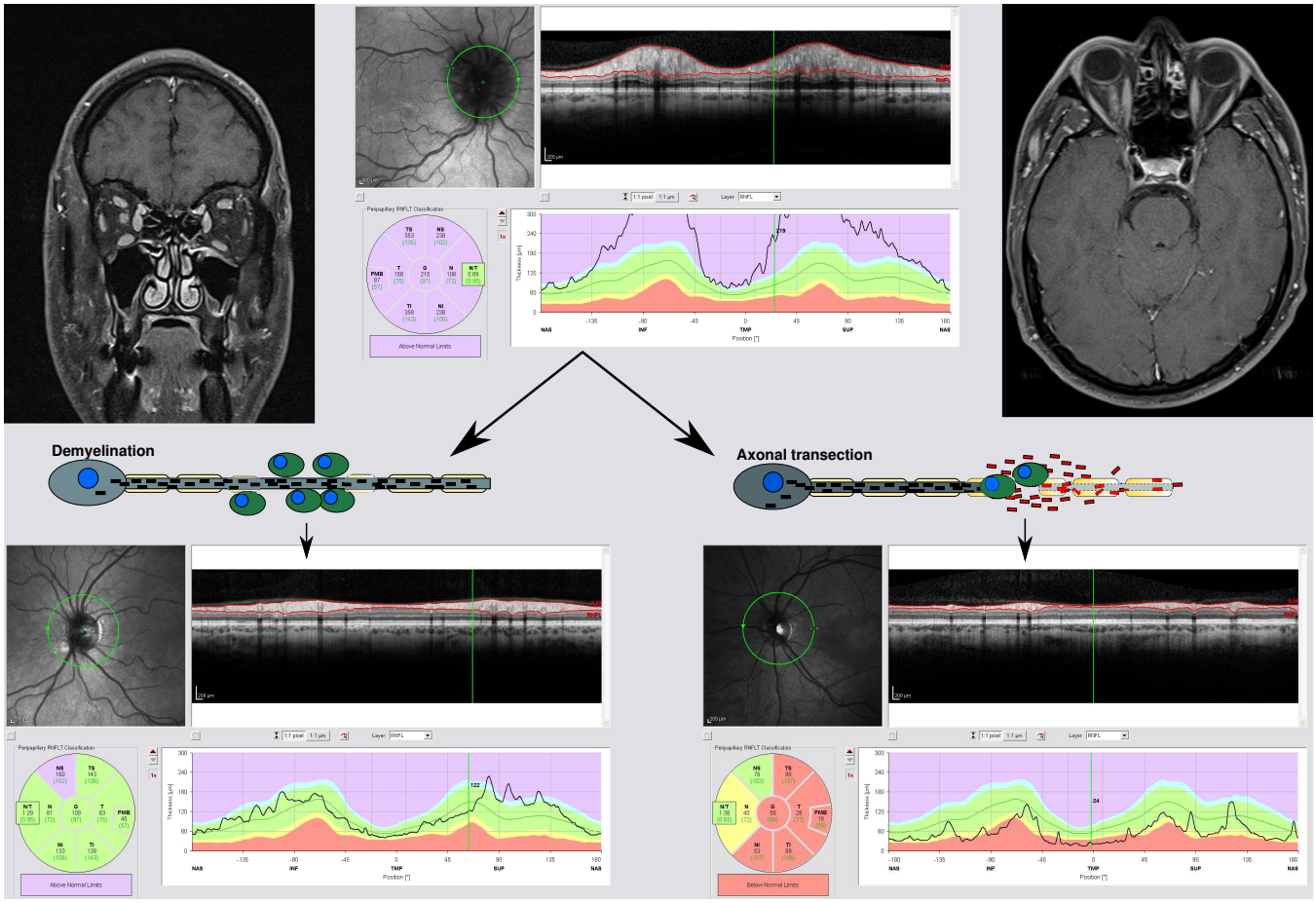

Figure 3: *A holistic model combining the strength of biomarkers suited for diagnosis (whole brain and spinal cord MRI) of the acute phase of neurodegeneration (e.g. body fluid neurofilament levels) with those more reliable during the later phase of neurodegeneration related atrophy measures (retinal OCT). A fundamental problem of imaging techniques is that any inflammation related oedema in the acute phase will mask neurodegeneration-related atrophy. Likewise, body fluid biomarkers such as neurofilaments will predominantly be released from disintegrating axons/neurons during the acute phase and only to a smaller degree during the "burnt out phase". A logical combination of these two distinct methodological approaches would be to have them integrated in longitudinal studies on neurodegeneration in MS.*

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