Molecular Imaging CRO Network

Micron's ViewPoint

Clinical Application of a Brain Image Analysis Program for Multiple Sclerosis

Part 3
Clinical Significance of "Brain Volume Visualization": A Treatment Strategy for Long-Term Prognosis

Contents

Introduction

What is the therapeutic goal of Multiple Sclerosis (MS)?

Among the various Disease-Modifying Drugs (DMDs) that can be selected at present, which DMD would be most suitable for each patient?

On the basis of considering these issues, the evaluation of brain volume is an important factor. Part 1 of a three part series of articles was an overview of MS, and part 2 described the evaluation of brain volume through brain image analysis programs. In this part 3, we will discuss how they are applied in actual clinical practice.

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The Natural Course of MS

In the diagnosis and treatment of MS, it is extremely important to understand "the natural course of MS" in advance by knowing what the patients will experience without treatment.

MS, known as a relapse and remitting disease, suggests a relationship between chronic inflammation and brain reserve capacity.[1] At the early stage of the disease, although the central nervous system, including the cerebrum has serious inflammation, most of the symptoms are not superficial because of the high brain reserve. However, in case the brain reserves gradually decline until can't no longer stand inflammation, the disease will relapse, making a variety of symptoms superficial, so that the accumulation will resulting obstacles (sequelae). Moreover, chronic inflammation is said to stabilize under the age of 50, but then accumulates with disorders in the central nervous system, whether or not relapse, will be accompanied by the worsening of symptoms, the so-called secondary progressive MS. Once it transitions into secondary progressive MS, regardless of the time of illness, the symptoms will generally worsen at a certain speed, gradually the patients will become wheelchair-dependent or even bedridden.[2]

From these points of view, it is clear that leaving MS untreated is the biggest factor in the worsening of symptoms.

Treatment Goals and Brain Atrophy

In clinical settings, we evaluate the changes of symptoms with: (1) relapse, (2) disability worsening and (3) the MRI activities, then treatment aimed at “without such symptoms”, that is to say NEDA (No Evidence of Disease Activity) -3 will be provided.[3,4] However, the index of NEDA-3 covers recognizable changes only. Therefore, it is considered very important to manage the symptoms of the disease from a deep understanding including factors that are difficult to assess such as the inflammation behind it and the increase of Neurofilament Light chain (NfL) suggestive of nerve damage [5], which is accompanied by it. Brain atrophy is the fourth factor, and NfL is the fifth factor. In recent years, they have been used as a target indicator of NEDA-4 and NEDA-5, respectively. (Figure 1)

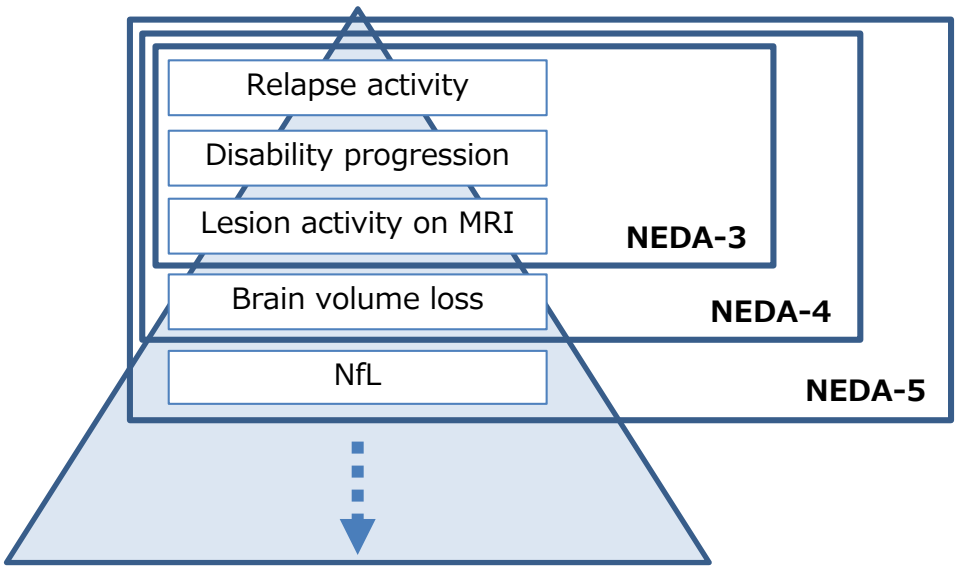

Figure 1. NEDA

Treatment Goals and Brain Atrophy

In fact, brain atrophy is observed with similar rate of changes as MS from CIS (Clinically Isolated Syndrome) which is the first clinical onset of potential MS [6], and it is known that it will progress regardless of relapse or not.[7] The association between brain atrophy and cognitive function has already been suggested.[8] In fact, from the early stage of the disease, high brain dysfunction led by attention disorder is often found in MS patients.[9] As the result, the quality of life (QoL) of patients have been known to decline.[10]

In one kind of MS, known as benign MS, the disease activity is very low, and there are few cases of relapse and the worsening of symptoms, but in most cases the natural course described above is followed. Therefore, if the long-term prognosis of the patient is taken into account, early diagnosis, risk assessment and appropriate treatment intervention are very important.

The Importance of Early Treatment Intervention and the Selection of DMDs

As of May 2021, there have been 8 types and 9 different DMDs for MS listed on the Japanese National Health Insurance Drug Price List, but their efficacy, safety, and route of administration varied. In the selection of drugs, we should follow the Shared Decision Making, that is, according to the patient's preferences and their lifestyle such as delivery. However, as a prerequisite, it is obligatory to provide sufficient information on drug selection: (1) the problem of long-term prognosis of selecting untreated, (2) the long-term efficacy and vulnerability of safety drugs, (3) the risk of complications associated with the selection of effective drugs and (4) the general description of complications and their countermeasures. On this basis, personal factors such as a male, the first diagnosed over 31 years of age or more than 3 relapses within 2 years after the onset of the disease are recognized as poor prognosis factors,[11] it is necessary to consider these factors together for DMD selection. Moreover, compared with administering good safety, but poor effect drugs, such as Interferon-β or Glatiramer acetate, the early administration of high effective drugs such as Natalizumab or Fingolimod, the probability of transition into secondary progressive MS was significantly lower.[12] Currently, there's a paradigm shift from a safety-oriented escalation therapy to a treatment strategy that selects highly-effective drugs at the early stage of the disease (induction therapy/rapid escalation therapy/early top down) with an eye to long-term prognosis.

The Importance of Early Treatment Intervention and the Selection of DMDs

If the NfL measurement, which represents the inflammatory results of the central nervous system, could be easily adopted as a stable value in clinical use, it would be a great help to the clinical practice. However, as it is now, the use of the NfL measurements are still unrealistic due to variabilities.5 Instead, brain atrophy caused by inflammation of the brain, including the cortex, is an important factor in the construction of treatment strategies. Brain atrophy indirectly shows the activity of the disease, and even in the absence of these poor prognostic factors, it can be judged that effective drugs are needed in patients with brain atrophy. In addition, it is considered that the advanced brain dysfunction found from the early stages of the disease cannot be compensated with metabolic capabilities after the detection of brain atrophy.[13] For this reason, taking into account the prognosis of the patient, the selection of Fingolimod and Natalizumab, which have a preventive effect on brain atrophy after the early detection of mild brain atrophy, is very important.[14, 15]

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Brain Image Analysis Programs in Clinical Practice

Natalizumab is one of the most effective drugs available at present.

Natalizumab is a drug that suppresses the binding of lymphocytes to VCAM-1 molecules found in vascular endothelial cells and hinders the migration of immune cells to the central nervous system, thereby stabilizing the immune state of the central nervous system.[16] On the other hand, it is known that it may cause a CNS (central nervous system) infection caused by JC virus, that is, Progressive Multifocal Leukoencephalopathy (PML) which cannot occur in healthy individuals.[17] In the case of PML complicated with HIV infection, the prognosis is poor as the central survival time is 1.8 years, but the PML associated with DMDs was about 20% or more.[17] In addition, various methodologies such as an occurrence prediction by using JCV index, or the early detection of lesion activity by MRI, which may avoid the worsening of the situation and have made it possible to avert risks.[18, 19]

As far as its efficacy is concerned, Natalizumab has been shown to have higher relapse inhibition rate, brain atrophy inhibition effect and EDSS improvement effect,[14, 20] and should be used more than ever in view of long-term prognosis. However, for most MS non-professional doctors and patients who evaluate the progression just with the relapse, compared with other DMDs, they often do not feel that the advantages of Natalizumab outweigh their disadvantages, so that Natalizumab will not be selected.

Then, by using the brain image analysis programs to evaluate the brain volume and switching to the treatment with recognition of the natural courses of MS and NEDA-4, it is expected that significant changes will occur in the choice of treatment and the long-term prognosis of the patients.

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Brain Image Analysis Programs in Clinical Practice

For example, case 1 (Male, around the age of 30; Figure 2) and case 2 (Female, around the age of 40; Figure 3) did not find obvious sequelae and high brain dysfunction, and only once clinical relapse found in the past, but there was already a significant difference from the average age of brain atrophy at the time of evaluation. Their respective poor prognostic factors are "male" for the case 1 and "the first onset over age of 31" for the case 2, but with the "brain volume visualization" of the brain image analysis programs, doctors and patients can jointly recognize the benefits of choosing effective drugs such as Natalizumab for treatment. This will be an opportunity to improve the quality of treatment.

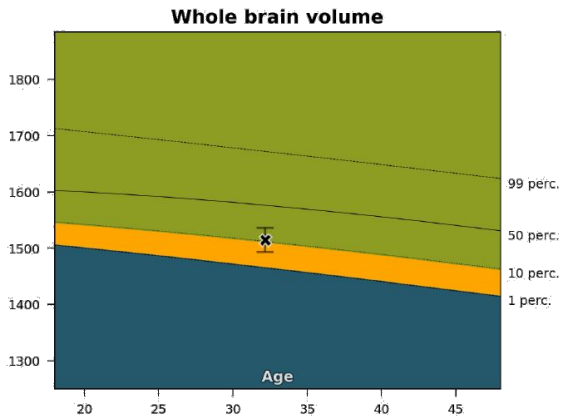

Figure 2. Male; around age of 30

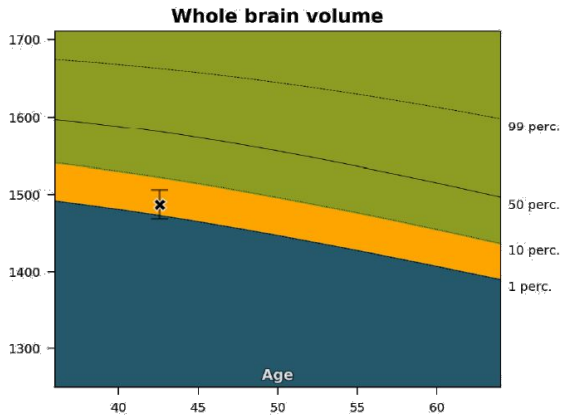

Figure 3. Female; around age of 40

Case 3 was a female, around the age of 50 (Figure 4), with abnormal sensations in her hands and feet, slight high brain dysfunction, and no relapse in recent years, but in the "brain volume visualization" of the brain image analysis program, it was identified as obvious brain atrophy. Considering her age, the de-escalation of DMD from the aspect of disease activity may be considered, but it is possible that the treatment strategy of secondary progressive MS may be taken into account by obvious brain atrophy, so as to select the Siponimod with brain sheath regeneration function.

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Brain Image Analysis Programs in Clinical Practice

As mentioned above, NEDA-3 had been a visible indicator so far, but NEDA-4 also become recognizable by using the brain image analysis program. Carrying out the treatment from the depth of the disease even if only slightly will bring a great impact on the long-term prognosis. Moreover, due to the differences in cognitive function in old age, in the future, patients' QoL need not be said, the medical expenses in the Japanese economy may also be reduced.

In recent years, very effective drugs can be used in the treatment of MS, and it is necessary to return the benefits to patients. In Japan, the brain image analysis programs are also gradually becoming more popular in the assessment of the condition of MS patients.[21] We expect the usage of the brain image analysis programs to become more widespread in the future.

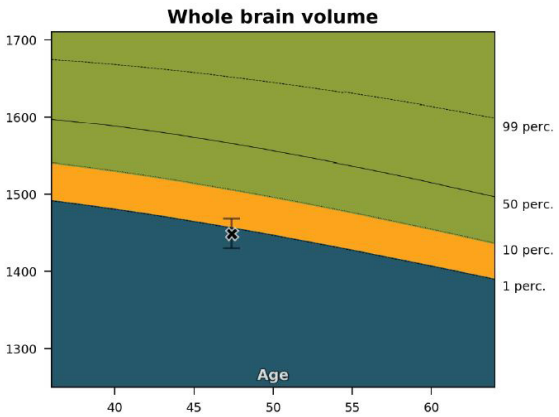

Figure 4. Female; around age of 50

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