Molecular Imaging CRO Network

Micron's ViewPoint

Clinical Application of a Brain Image Analysis Program for Multiple Sclerosis

Part 1

Multiple Sclerosis and Diagnostic Imaging

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Introduction

Studies on multiple sclerosis (MS) have been making progress in recent years. There have been findings on elucidating the pathogenesis, new therapeutic agents being developed one after another, and the therapeutic goals have largely changed accordingly. In the midst of this paradigm shift, we will discuss the significance of brain volume measurement using a brain image analysis program in this three-part paper..

Kenzo Sakurai

Current Position	Senior Lecturer, Department of Neurology, St. Marianna University School of Medicine Medical Director, Department of Neurology, St.Marianna University School of Medicine Hospital
Biography	Graduated from St. Marianna University School of Medicine in 2005
Qualifications	Board Certified Physician, Specialist in General Internal Medicine and Supervising Physician (The Japanese Society of Internal Medicine) Board Certified Specialist and Supervising Physician (Japanese Society of Neurology) Board Certified Specialist and Supervising Physician (Japan Society for Dementia Research) Board Certified Specialist and Supervising Physician (The Japanese Headache Society) Board Certified Specialist and Supervising Physician (The Japan Stroke Society)
Area of Expertise	Multiple Sclerosis, Neuromyelitis Optica, Myasthenia Gravis, Neuroimmune Diseases

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Multiple Sclerosis

MS is a chronic inflammatory demyelinating disease characterized by multiple spatial and temporal manifestations. In Japan, there has been a rapid increase in the number of patients in recent years. A nationwide epidemiological survey conducted in 2019 showed that the number of patients has doubled in the past 15 years to approximately 20,000.[1] The cause of the disease is not clear. There are reports suggesting that genetic factors such as human leukocyte antigen (HLA) are involved. In addition, environmental factors such as smoking, vitamin D, and EB virus infection are reported to be related. The intestinal bacteria due to dietary changes has been suggested as one of the reasons for the rapid increase in recent years.[2-5]

MS is commonly diagnosed in young people around the age of 30 years old. It is characterized by the relapse and remission of symptoms. As a result of inflammation in the central nervous system including the brain and spinal cord, the myelin sheath surrounding the nerve cells is damaged, which is called “demyelination”. As a result of demyelination, the symptoms emerge such as motor paralysis, sensory disturbance, vision loss, and urinary disorder. As shown in Figure 1, in the early phase of MS, the symptoms appear to remit from the body’s natural healing. However, as the duration of disease becomes longer prolongs, the brain reserve capacity gradually decreases; this results in insufficient recovery, and lasting after-effects. If such a condition continues to progress, then so will the disease, with or without relapse. In addition, studies in recent years have shown that if the inflammation of the central nervous system is severe in the early phase, the higher brain dysfunctions, including brain atrophy and attention deficit will often be observed even when the degree of relapse is mild.[6, 7] Based on such evidence, the treatment for MS is shifting from escalation therapy, in which safety is prioritized and patients are switched to stronger drugs when disease activity cannot be controlled, to induction therapy, in which drugs with high therapeutic efficacy are introduced from the beginning.

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Multiple Sclerosis

What is the index of MS treatment? In general, it is considered to be the achievement of NEDA (No Evidence of Disease Activity)-3, which is defined as absence of relapses, disability worsening, and MRI activity. In recent years, missing the brain volume loss (lack of brain atrophy) is added as one of the indices to be NEDA-4, and the suppression of neurofilament light chain elevations ad ded as NEDA-5.[8] The update of the treatment index is ongoing. However, it is currently impossible to measure all the above biomarkers in actual clinical practice. For example, the brain atrophy accessed by brain volume measurement mentioned above has not yet been applied in clinical.

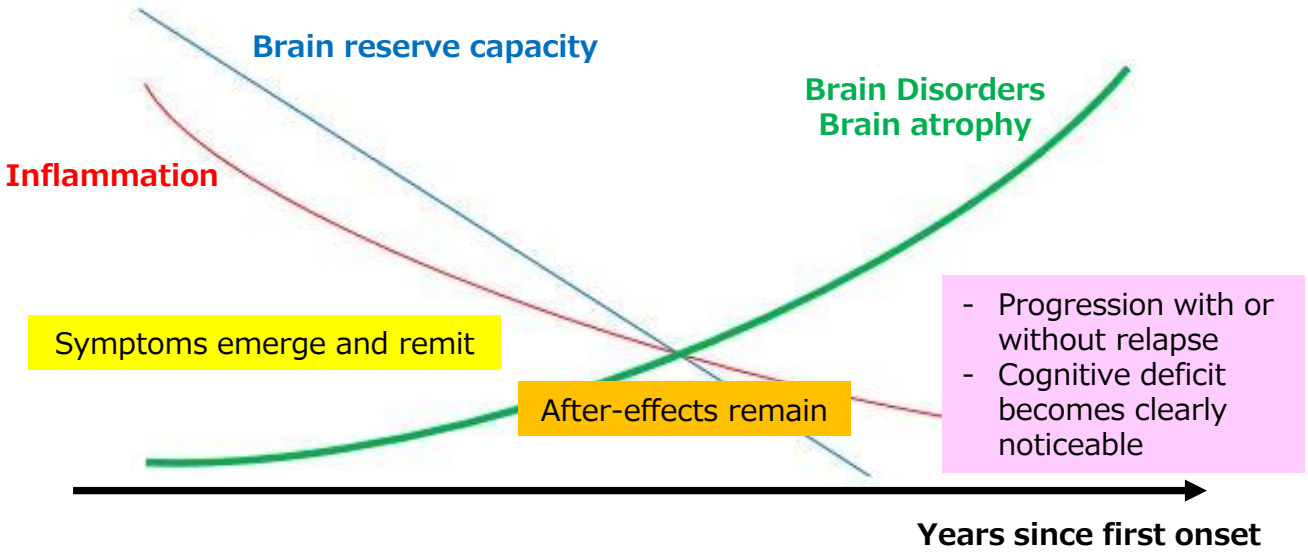

Figure 1: Progress of Multiple Sclerosis

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Diagnostic Criteria

Currently, the diagnostic criteria for MS used are the 2017 revisions of the McDonald criteria (Figure 2). [9] Comparing to the previous 2010 McDonald criteria, the 2017 revisions improved diagnostic sensitivity and enabled diagnosis of MS early phase. Other changes include the CSF oligoclonal bands (OB) positive can be substituted for dissemination in time, and the symptomatic lesions can be counted as a focus. In addition, since there is no emphasis on excluding other diseases, it is important to distinguish MS-like syndromes in light of other diagnostic criteria.

Relapse Times	Number of Lesions	Additional Data Needed for Diagnosis
Two or more times	Two or more	None
	One	Relapse in different regions or DIS by MRI (magnetic resonance imaging)
Once	Two or more	Relapse, MRI evidence of DIT, or CSF OB positive
	One	Relapse in different regions or MRI evidence of DIS and Relapse, MRI evidence of DIT or CSF OB positive

Dissemination in Space (DIS)	Dissemination in Time (DIT)
Recurring in over two of the four regions of the central nervous system (periventricular, cortical or near-cortical, sub-tentorial, and spinal) and one or more T2 high-signal lesions.	• The simultaneous presence of gadolinium contrast-enhancing and non-gadolinium contrast-enhancing lesions. • The appearance of new T2 high-signal lesions or gadolinium contrast-enhancing lesions when compared to the reference MRI.

Figure 2. Excerpt of the McDonald Criteria 2017

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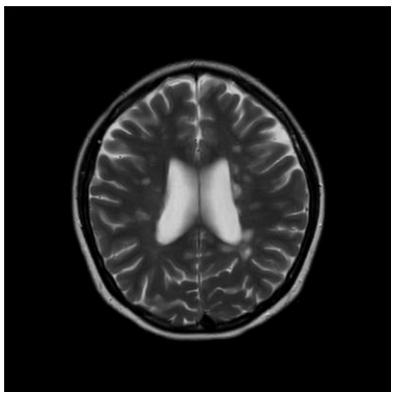
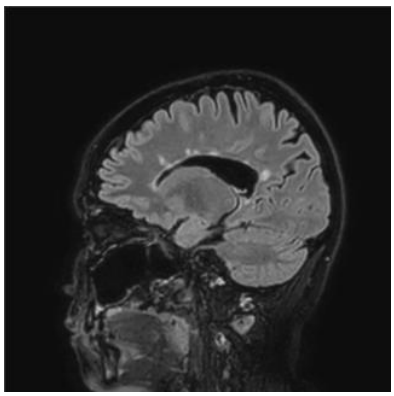
Imaging Tests

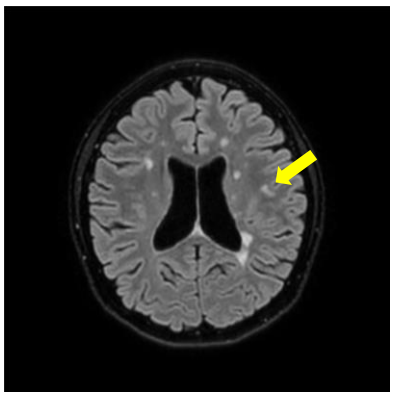
The diagnosis of MS is established by proving DIS, DIT, and the exclusion of other diseases. An MRI scan is useful in confirming MS-like features. For example, ovoid lesions, which are oval deep white matter lesions extending vertically around the lateral ventricle, are a common finding, although they do not have high specificity for MS (Figure 3).[10] Callosal-septal interface lesions, which extend vertically from the lower part of the corpus callosum, are an imaging finding typical of MS with high sensitivity and specificity. Central vein signs, in which veins penetrate the lesions, and the juxtacortical lesions, which extend along the subcortical white matter, are also frequently seen.[11] Spinal cord lesions are most likely to be seen in the cervical spinal cord, and lesions are often localized to the limbic region.[12] Lesions extending over three vertebrae or covering the entire spinal cord are not typical of MS, but rather are suspicious of other diseases such as neuromyelitis optica. In recent years, the DIR (double inversion recovery) method has facilitated the identification of cortical lesions. Therefore, cortical lesions are listed as one of the DIS regions in the McDonald Criteria 2017. Cortical lesions are known to be associated with cerebral atrophy and higher brain dysfunction.[13] They are one of the critical findings for long-term prognosis.



Ovoid Lesion
(T2-weighted image)



Callosal-septal Interface Lesion
(FLAIR Image)



Juxtacortical Lesion
(FLAIR Image)

Figure 3. MRI Findings of MS

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Treatments

Currently in Japan, there are seven types of disease-modifying drugs and eight formulations to choose from, starting with betaferon, launched in 2000, and ending with mayzent, launched in 2020. (Table 1)

Brand Name	Tysabri®	Gilenya®	Tecfidera®	Betaferon®	Avonex®	Copaxone®	Mayzent®
Generic Name	Natalizumab	Fingolimod	Dimethyl fumarate	Interferon beta		Glatiramer acetate	Siponimod
Route of Administration, Administration Frequency	IV drip, Once in 4 weeks	Oral, Once a day	Oral, Twice a day	SC injection, Once in 2 days	IM injection, Once a week	SC injection, Daily	Oral, Once a day
Effect	Very strong	Strong	General	Weak		Weak	Strong
Safety	Slightly low	Slightly low	General	High		High	Slightly low
Main Side Effects	PML	PML, Herpes zoster, Lymphocytopenia	Abdominal pain, Diarrhea, Lymphocytopenia	Influenza-like symptoms, Depression		Injection site reaction	PML, Herpes zoster, Lymphocytopenia
Administration to Pregnant Woman	In some cases	Avoid	In some cases	In some cases		Suitable	Avoid
Preventive Effect of Brain Atrophy	Yes	Yes	Yes	No		No	Unknown
Other	Possible rebound due to drug withdrawal		Careful dose increase at the time of introduction	-		-	Adapted for secondary progressive type

PML : Progressive multifocal leukoencephalopathy

Table 1. Disease-Modifying Drugs for MS

Regarding MS treatment, there is no objection to early diagnosis and early initiation of treatment. Nevertheless, it has not been established yet which to use first: the drugs which are safer, such as interferon beta and glatiramer acetate, or the drugs which are more effective, such as natalizumab and fingolimod. The mainstream induction therapy in the past was to emphasize safety. The reason is that even with a weak effect it is still effective in preventing relapse. However, it is now known that although relapse can be inhibited, brain atrophy cannot. Since brain atrophy is a change observed from the early stage of the disease, the induction therapy is shifting to use stronger drugs and the potential to inhibit brain atrophy from the early stage of the disease.[14] The goal of treatment is thus shifting from prevention of relapse to treatment with a long-term prognosis in mind.

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Treatments

Brain atrophy is one of the changes in the brain that directly leads to higher brain dysfunction. It has been known that brain atrophy progresses faster in MS patients than in normal people, at about 0.9% per year, compared to about 0.2% per year in normal people.[15] It remained a challenge to assess brain atrophy in clinical practice. Even though the change of 0.9% is difficult to notice by visual assessment, the assessment such as the degree of brain atrophy at the time of diagnosis and the amount of change related to brain atrophy over 1 to 2 years has to be judged by the attending physician. This has proven to be lacking in objectivity. Nevertheless, the choice of treatment for brain atrophy had to be made based on the physician's subjective judgment, or after the brain atrophy had clearly worsened after nearly 10 years. The brain is a precious organ that is unable to recover sufficiently from any kind of damage, including brain atrophy. It is more and more accepted that intervention for brain atrophy of MS should be entered in an early phase when the brain atrophy has not exacerbated.

A brain image analysis program can provide reference of brain volume in a manner of mean value by age, so it may help to identify the status at the time. In addition, by a serial assessment over time, it can work as an objective measurement tool to provide results such as brain atrophy rate by year. A brain image analysis program is becoming popular for the disease assessment of MS patients in Japan as well and enables objective measurement and analysis of brain volume which was impossible in clinical practice.[7] This is considered to be very useful as a new biomarker for MS treatment.

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