Molecular Imaging CRO Network

Micron's ViewPoint

Clinical Application of a Brain Image Analysis Program for Multiple Sclerosis

Part 2

The Usefulness in Multiple Sclerosis Treatment: Potential of Being a Part of a New Evaluation Scale

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Introduction

The treatment goal of multiple sclerosis (MS) has shifted from suppression of relapse to a better long-term prognosis based on recent research results. Especially, the suppression of brain atrophy has become an important factor. As mentioned in part 1, multiple sclerosis and diagnostic imaging, the evaluation method for brain atrophy in MS has not been established. In part 2, we would like to discuss the possibility of using a brain image analysis program as a new evaluation method based on a few actual cases.

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Area of Expertise	Multiple Sclerosis, Neuromyelitis Optica, Myasthenia Gravis, Neuroimmune Diseases

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Analysis Report Features

A brain image analysis program the author uses performs quantitative analysis of brain volume based on head MR images. It is able to conduct both quantitative analyses of whole brain volume and gray matter volume. Those volumes for the specific subject and the average by age are presented not only by the actual values but also on a graph. This helps to make it easy to understand the difference between the subject results and the average values, even only at a glance.

In addition, the quantitative analysis of the MS lesion volume is also performed. As a result, the volume value of the high signal region in the FLAIR image and the low signal region in the T1-weighted image are also presented in the report. As for the high signal area in FLAIR image, the volume is shown as divided into periventricular, paracortical, infratentorial, and deep white matter. If there are follow-up tests over time, the values from different visits will be arranged in a chronological order to make the changes over time easy to understand.

Advantages and Challenges of Applying a Brain Image Analysis Program in Clinical Practice

It is known that brain atrophy of MS appears from the early stage of the disease and develops to progression regardless of relapse.[1, 2] In fact, it has been suggested that suppression of relapse may not affect the long-term functional prognosis.[1] Therefore, we have to admit it is insufficient to only achieve the previous treatment goal of NEDA-3 (No Evidence of Disease Activity), which is defined as absence of relapses, disability worsening, and MRI activity.

It has been suggested that the suppression of brain atrophy and neurofilament light chain (NfL) are necessary when the long-term prognosis is taken into consideration.[3, 4] However, it remains difficult in clinical practice to evaluate brain atrophy. We recognize this as a critical point for MS treatment. In fact, the various evaluating methods for brain atrophy have been tested on their correlation with brain volume, such as the third ventricular diameter, the thickness measurement of RNFL (Retinal nerve fiber layer) by OCT (Optical coherence tomography) examination, and corpus callosum index value. However, none of them have been established as a validated biomarker at the moment.[5, 6] In addition, these indicators are used only by some MS specialists. Generally, neurologists compare two or more MR images taken over time in order to evaluate brain atrophy. Since such evaluation is only based on visual judgment, it has the risk of subjective assessment bias. As a result, the diagnosis of brain atrophy may often take up to 10 years, and in most cases, it is only a retrospective diagnosis, not an indicator of intervention.

Advantages and Challenges of Applying a Brain Image Analysis Program in Clinical Practice

In considering the long-term prognosis of MS, adverse prognosis factors such as male subjects or elderly-onset will be evaluated,[7] and it is critical to evaluate the brain atrophy as part of disease activity evaluation as well. As explained in part 1, since there are few treatment choices if diagnosed after progression, it is important to determine brain atrophy at an early stage. As analysis results comparing the average of healthy subjects are provided on the report of the aforementioned brain image analysis program, it enables the evaluation of the state of brain volume from an early stage of the disease. It is a useful test that should be performed as soon as MS diagnosis in order to develop a treatment strategy that takes into account the long-term prognosis. In addition, the report can provide the result of change rate over time when tested multiple times, which may be used as one of the factors to be considered for treatment alternation. Therefore, it is a test that should be repeated over time.

Although a brain image analysis program is becoming popular for the disease assessment of MS patients in Japan as well,[8] there are a few remaining issues when applying brain image analysis programs in clinical practice. First of all, the evaluation by brain image analysis programs is not included on the medical insurance list in Japan at present. The situation is that it is only available in some facilities. The second issue is the racial differences in brain volume. Since brain atrophy is judged by comparison with the mean value, and the mean value varies greatly depending on the race, it is urgently needed to establish the mean value for each race. The last issue concerns evaluating changes over time. Since the amount of brain atrophy is very small, if different conditions are used in scanning, deviation errors may happen accordingly and make it difficult to judge the true result. For example, the analysis results may vary widely from visit to visit, due to the differences in MRI scanner, or before and after steroid pulse therapy. Therefore, it is necessary to establish imaging conditions and imaging intervals for MRI in the future.

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Advantages and Challenges of Applying a Brain Image Analysis Program in Clinical Practice

Although several issues remain at this stage, considering there are few means by which brain volume can be measured, and it can be a very important index in considering the long-term prognosis in the initial stage of the disease, we would still like to propose brain image analysis program reports as useful tools in clinical management.

Examples of Reports of a Brain Image Analysis Program in Clinical Practice

Here, we present two cases in which brain volume was measured by a brain image analysis program, in order to provide examples of practical application methods in clinical practice. The examples are only for reference. Considerations and treatment options are not necessarily the same. Consent was obtained from the two patients included.

Case 1: A 41-year-old man; a brain image analysis program used for evaluation of brain volume at the time of diagnosis and helped with the choice of the disease-modifying drugs

The patient developed left homonymous hemianopsia at the age of 41. He was diagnosed with MS based on brain MRI and cerebrospinal fluid examination. There was no similar onset in the past, so it was clinically judged as the primary onset. MS can be divided into the inflammatory phase and the degenerative phase. It is reported that the inflammatory phase that can be intervened in the treatment of relapsing-remitting MS is around 45 years of age.[9] In this case, the patient will reach the intervention point in 4 years. In addition, the two factors of the male and first episode over age 31 are known as poor prognostic factors.[7] An analysis was performed using a brain image analysis program as a reference for selecting disease-modifying drugs.

As the analysis report shows (Figure 1, Figure 2), although generalized brain atrophy was observed in comparison with relative age, the degree was judged to be moderate. Based on such a result, disease activity was judged as not high. Therefore, despite the poor prognostic factors, natalizumab and fingolimod, which are highly effective drugs but requiring attention to prevent adverse reactions, were not selected. Interferon beta (IFN β) and glatiramer acetate, which have been proven to be safe for long-term but have a limited inhibitory effect on brain atrophy, were not selected because brain atrophy was actually observed. As a final decision, treatment with dimethyl fumarate, which has an inhibitory effect on brain atrophy and balances the efficacy and adverse reactions, was initiated.[10, 11]

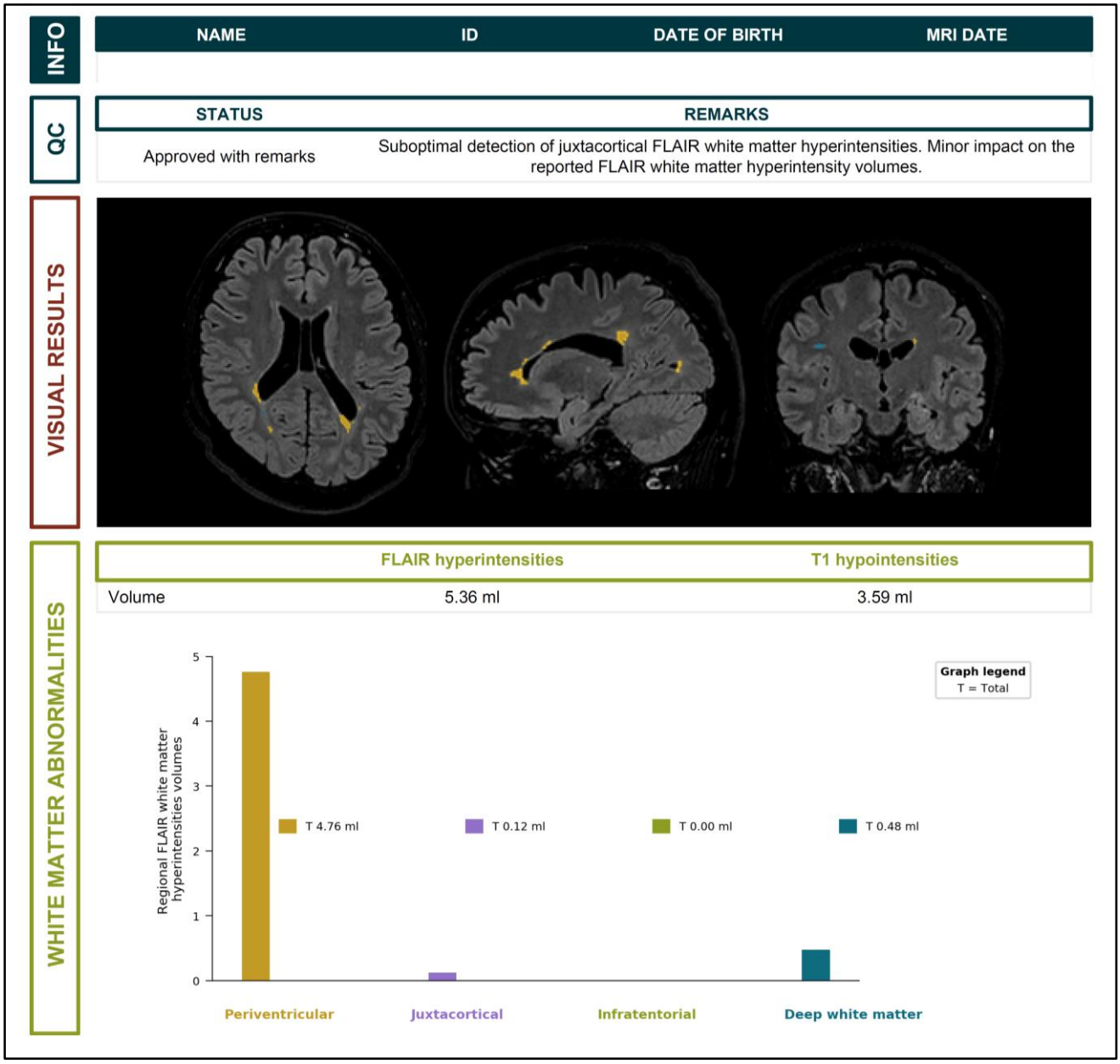

Figure 1. The Report of a Brain Image Analysis Program
for Case 1 of a 41 Year-old Man, Page 1

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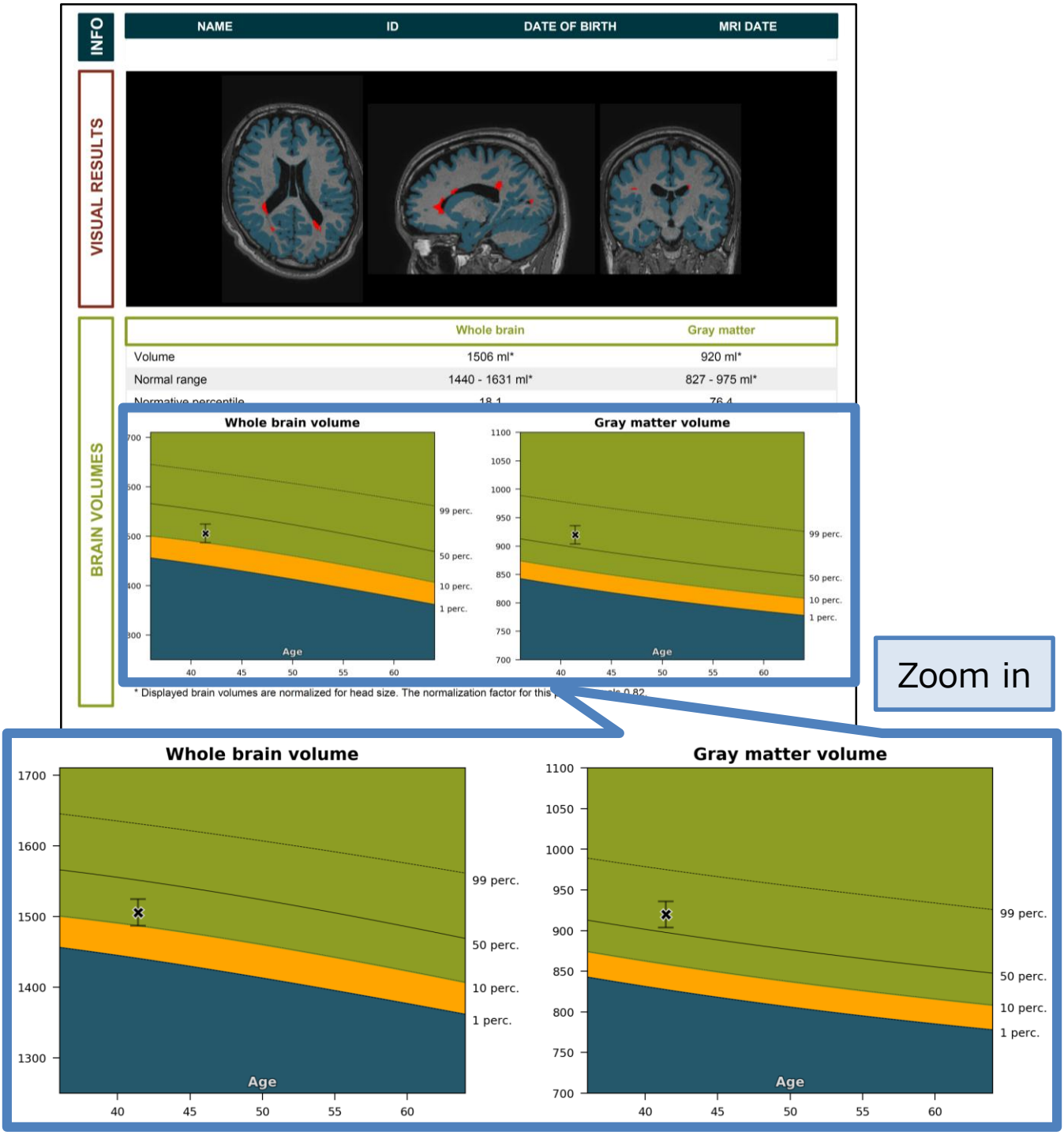

Figure 2. The Report of a Brain Image Analysis Program for Case 1 of a 41 Year-old Man, Page 2

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Examples of Reports of a Brain Image Analysis Program in Clinical Practice

Case 2: A 35-year-old woman treated with IFNβ-1a without relapse or aggravation

The patient developed dysesthesia of the right lower extremity at the age of 32. After diagnosis, steroid pulse therapy was performed, and IFNβ-1a was introduced. Since then, the head MRI examination was performed every half year. There has been no MRI activity, and no observed clinical findings suggesting relapse or aggravation. In addition, there were no subjective symptoms reported leading to a decline in work efficiency. At the age of 35 (3 years after onset), brain atrophy was assessed by a brain image analysis program based on the head MR images. The result suggested remarkable general brain atrophy in comparison with the relative age. (Figure 3, Figure 4)

Based on such results, treatment changes from IFNβ-1a to another disease-modifying drug were discussed, since IFNβ-1a has no inhibitory effect on brain atrophy. The symbol digit modalities test (SDMT) was conducted as an additional test, in order to evaluate the patient's visual information processing speed and working memory. The results suggested appropriate for the patient's age. In consideration of future life events including childbearing, it was decided not to change the disease-modifying drug at this stage, but to continue to evaluate the brain atrophy and higher brain dysfunction periodically in order to consider treatment shift as appropriate.

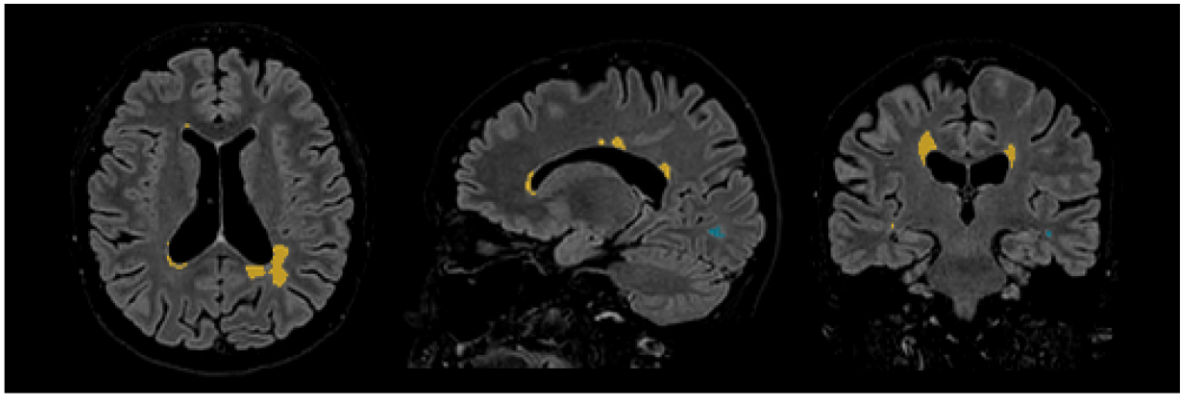
INFO

NAME	ID	DATE OF BIRTH	MRI DATE

QC

STATUS	REMARKS
Approved	No remarks.

VISUAL RESULTS



WHITE MATTER ABNORMALITIES

	FLAIR hyperintensities	T1 hypointensities
Volume	6.74 ml	4.60 ml

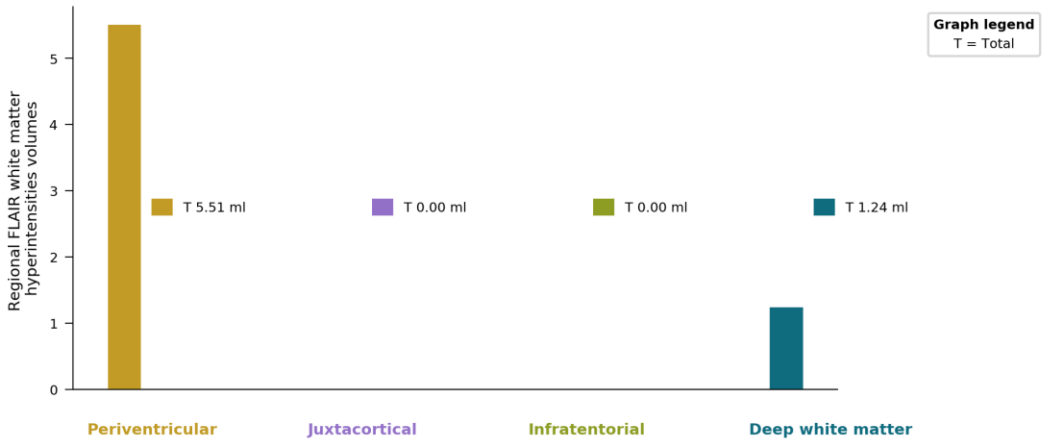


Figure 3. The Report of a Brain Image Analysis Program for Case 2 of a 35 Year-old Woman, Page 1

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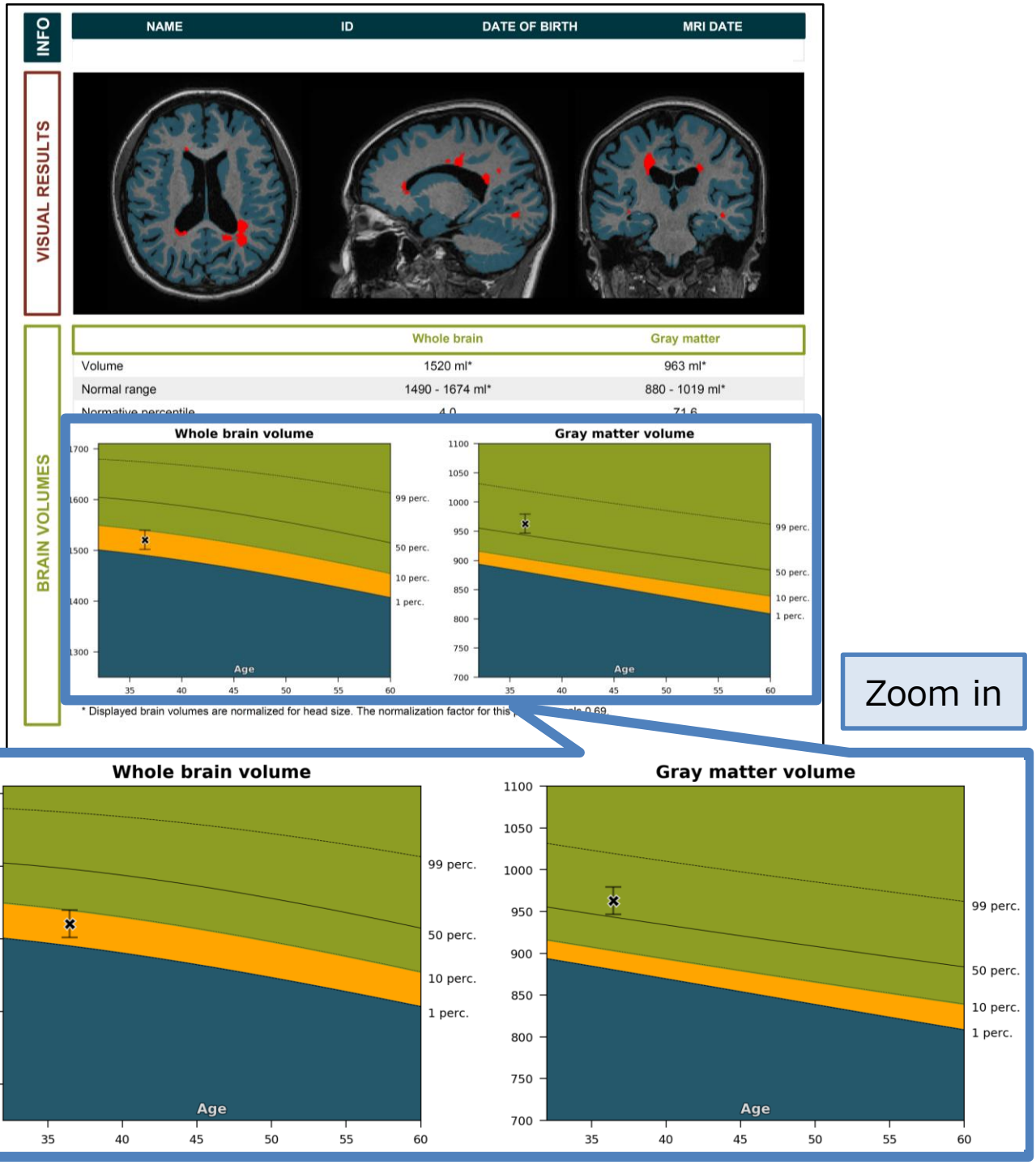

Figure 4. The Report of a Brain Image Analysis Program for Case 2 of a 35 Year-old Woman, Page 2

Examples of Reports of a Brain Image Analysis Program in Clinical Practice

In summary, what is common throughout the above two cases is that the analysis report should be considered as one of the reference materials for drug selection or changes, but not the only factor in decision making. However, the analysis report may provide critical support for decision making. As it is shown in case 1, if brain atrophy assessment could not be quantified, it is possible that the patient would have had to choose a drug with high efficacy but worry about the extra side effects that come along with it. In case 2, it is possible that the patient might have been preoccupied with relapse and delayed the necessary cognitive assessment.

We understand the larger the amount of clinical information, the more benefit the patient will receive. In the case of MS management, it is common for MS patients to undergo periodic head MRI examinations. If we can quantify the brain volume based on the MR images, it will make a huge difference in the amount of information. There are issues that remain yet to be discussed in the future, such as the long-term prognosis difference due to the changes of the brain volume, and the evaluation method of the change over time. However, as the examples imply, the brain volume evaluation by a brain image analysis program at the time of diagnosis or during the progress may provide necessary reference information for improving the quality of the medical care. Although a program is available only in some facilities in Japan at present, it is recommended to have this as an available test for the whole population.

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