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Distribution of brain plaques in patients with clinically definite Multiple Sclerosis diagnosis in Kerman city

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ABSTRACT

In this study we investigated the distribution of brain plaques in patients with clinically definite Multiple Sclerosis diagnosis in Kerman city. So 126 patients with clinically definite Multiple Sclerosis diagnosis in Kerman city were enrolled in the study. The patients were those registered at the Iran Multiple Sclerosis Society, Kerman branch and the diagnosis was based on McDonald revised Criteria. All the patients subjected to T2W and FLAIR Brain MRI. The most common anatomic location of MS plaques was centrum semiovale and juxtacortical and subcortical white matter except the periventricular area (53.96%) and the rarest location was cerebellum (1.89%).No relationship was observed between the anatomical distribution of Multiple Sclerosis plaques and age and duration of disease but there was a relationship between sex and distribution of MS plaques in Brain MRI except the cerebellum and the pons. ($p<0.05$)

Key words: Multiple Sclerosis, MRI, FLAIR, T2W, Plaque, Distribution, Age, Sex, Duration of disease

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INTRODUCTION

Multiple Sclerosis is a demyelinating disease of CNS. The disease usually begins between the ages of 15 and 50 and the most common age for developing MS is 30 years.

The ratio of the disease between female and male is considered as F: M ratio of 2-3:1 and there is also seen a special geographical distribution in this disease; in other words MS is more common in areas further away from the equator (1).

Epidemiologically, the occurrence of MS in Kerman province is reached to about 31.5% per 100000 people and 57.3% per 100000 people of Kerman City (2). Multiple sclerosis is inherited as a complex multifactorial disorder that results from the interaction of genetic and environmental factors. The risk of the disease between siblings is estimated as 3%-5%, increasing to 29.5% when one or two of parents have MS. (3).

In a study (4) on 44 meta-analysis including 416 researches on the effective environmental factors in MS, it is specified that the environmental factors including vaccination, disabling diseases, trauma and infections can be very effective in the formation of MS specially In people with genetic susceptibility to MS. Since it seems that the genetic and environmental factors are very effective in the occurrence of MS (3) and they may also have effects on the plaques distribution; so, Evaluation of plaque distribution pattern in each geographic region is valuable.

Diversity of MS clinical presentations are because of diversity in anatomical distribution and number of MS plaques over time and space. Generally, 4 clinical courses are described for MS (5-6):

1. relapsing–remitting

- most common (70% of cases)
- patients exhibit periodic symptoms with complete recovery (early on)

2. secondary progressive
- approximately 85% of patients with relapsing-remitting MS eventually enter a secondarily progressive phase

3. primary progressive
- uncommon (10% of cases)
- patients do not have remissions, with neurological deterioration being relentless

4. progressive with relapses

As it mentioned, different forms of MS have overlaps with each other and it may be even changing to another form in a patient over the time. The symptoms may be sensory, motor or both of them resulting from involvement of different parts of CNS by MS plaques. Ovoid Shape MS Plaques are mostly seen in Periventricular areas (7). Radiologic diagnosis of MS is based on McDonald's revised criteria (8). The standard method for screening the brain plaques is MRI. The radiologic features of MS plaques in MRI are as following (9-10-11-12):

- **T1**
  - lesions are typically iso- to hypointense (T1 black holes)
  - callososeptal interface may have multiple small hypointense lesions (Venus necklace) or the corpus callosum may merely appear thinned hyperintense lesions are associated with brain atrophy and advancing disease
- **T2:** lesions are typically hyperintense
- **FLAIR**
  - lesions are typically hyperintense
  - very early sign is called "ependymal dot-dash sign": alternating small foci of hyperintensity along the callososeptal interface
  - when these propagate centrifugally along the medullary venules and arranged perpendicular to lateral ventricles in triangular configuration (extending radially outward -best seen on parasagittal images), they are termed Dawson fingers
  - FLAIR is more sensitive than T2 in detection of juxtacortical and periventricular plaques while T2 is more sensitive in infratentorial lesions
- **T1 C+ (Gd)**
  - active lesions show enhancement
  - enhancement is often incomplete around the periphery (open ring sign)
- **DWI/ADC:** active plaques may demonstrate restricted diffusion
- **MR spectroscopy**
  - NAA peaks may be reduced within plaques, which is the most common and remarkable finding
  - Cho and lactate are found to be increased in the acute pathologic phase

Since there has not been carried out any investigation on the distribution of MS plaques in Kerman Province and unfortunately, a large population suffer from this disease in this province (2) we aimed at evaluating the main pattern of anatomical distribution of MS plaques in the brain in this district because each plaque makes a clinical symptom in the brain (13-14). If significant differences exist between the anatomical distributions of plaques in different geographic areas with different genetic and environmental characteristics, such surveys would be a valuable assistance for the neurologists in each region for establishing long-term treatment plan of the patient.

A review of articles:

Today the application of MRI images in MS is one of the most common approaches. In the revised Criteria of McDonald as the latest diagnostic Criteria for MS disease, it is stated that MRI is the technique of choice for evaluation of dissemination of MS lesions in time and space, in other words, by this method the activity of MS can be evaluated. (15) Because, even when these lesions cause no clinical symptoms, MRI is able to identify them. The MS plaques are usually appeared as asymmetrical periventricular hyper intense lesions in MRI. Brain plaques, even a large number, are usually asymptomatic. Periventricular lesions are also seen in other diseases and elderly but these lesions are hypo intense. The most diagnostic feature in MS lesions are ovoid or linear demyelinated areas, vertical to the ventricles, along with periventricular white matter radial fibers. (16). Some MS cases have been reported with demyelinating processes mimicking a tumor of the central nervous system (17).

First, Mr. Jung in 1981 spoke of the effectiveness of MRI in diagnosis of MS and suggested that the application of this method can be very useful in all therapeutically studies (18). Since then and particularly in the recent years most therapeutically trails of MS have been evaluated by MRI.

2. In a study on the role of MRI in the diagnosis and follow-up of MS, It was found that because of its unique sensitivity in the diagnosis of central nervous system demyelinating plaques, MRI is the method of choice in radiologic diagnosis and follow up of MS. (19)
3. In another study over 145 patients with MS, it is concluded that Hyper intense MS plaques on T1-weighted MR images are common and associated with brain atrophy, disability, and advancing disease so that the Hyper-intense lesions may be considered as a clinical bio-marker in this regard (20).
4. Other study (21) on the gray matter of brain of MS patients, it was specified that the brain gray matter lesions are mostly seen in: Hippocampus and Parahyppocampus (9.1%), insula (8.9%), cingulated cortex (8.3%), superior frontal gyrus (8.1%), and cerebellum (6.5%).
5. In a descriptive cross-sectional study (22), it was concluded that it is not possible to predict the severity of symptoms of MS just according to the MRI results, but study of both factors simultaneously is necessary in proper evaluation and diagnosis of the disease.
6. In a study (23), it is seen that the MS plaques could be seen in juxtacortical, infratentorial, periventricular, deep white matter, mixed white-gray matter areas.

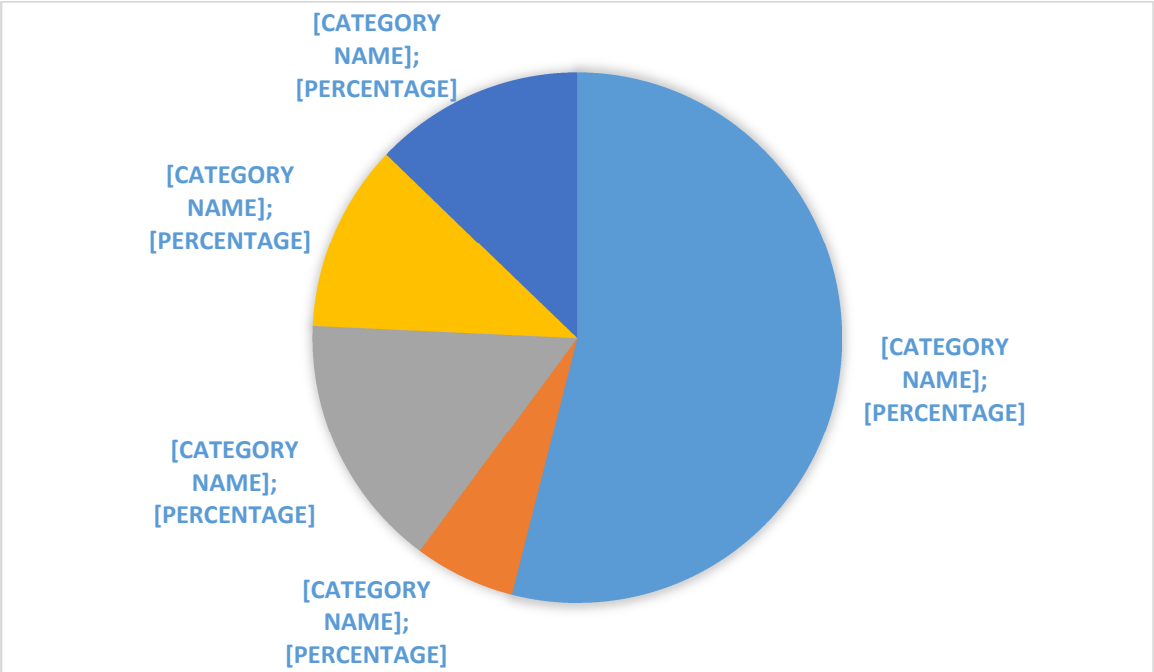
MATERIALS AND METHODS

This is a cross-sectional study. The studied population were MS patients referred to Besaat clinic in Kerman city. T2W and FLAIR MRI images were obtained from all the patients.

Patients with definite diagnosis of MS by neurologist were entered into the study. From these patients, who could not underwent MRI (patients with Cardiac Pace Maker, intracranial aneurysm clips and ...), were excluded from the study.
Sex, age and duration of disease (since the time of definite diagnosis by neurologist) were collected from all the patients in the study. All the Brain MRIs have been performed by Siemens Avanto B15, 1.5T in Besaat Clinic.

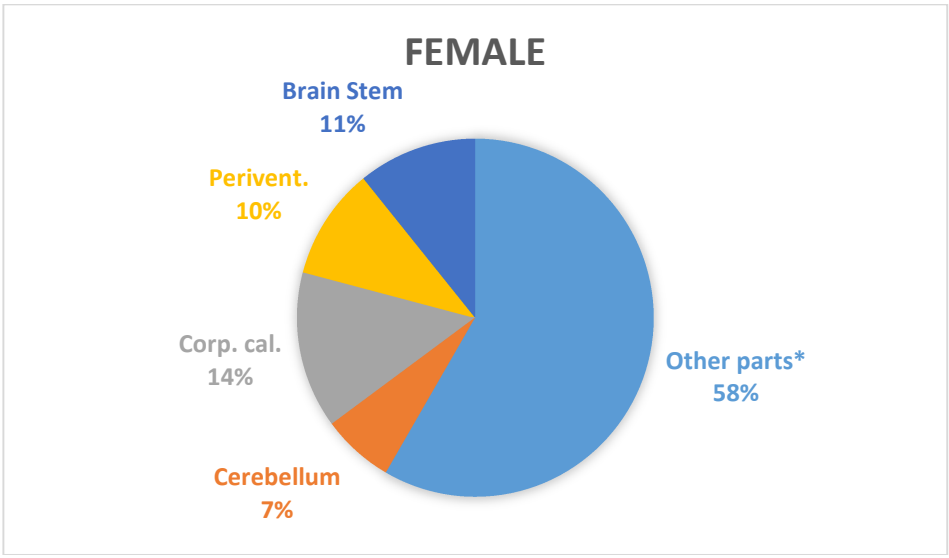
SPSS20 Software was applied for analyzing the data of the study. The distribution and relative distribution and mean central index are also applied as the descriptive statistics and K analytical test or Fischer test and T-independent test are also applied for the analytical statistics.

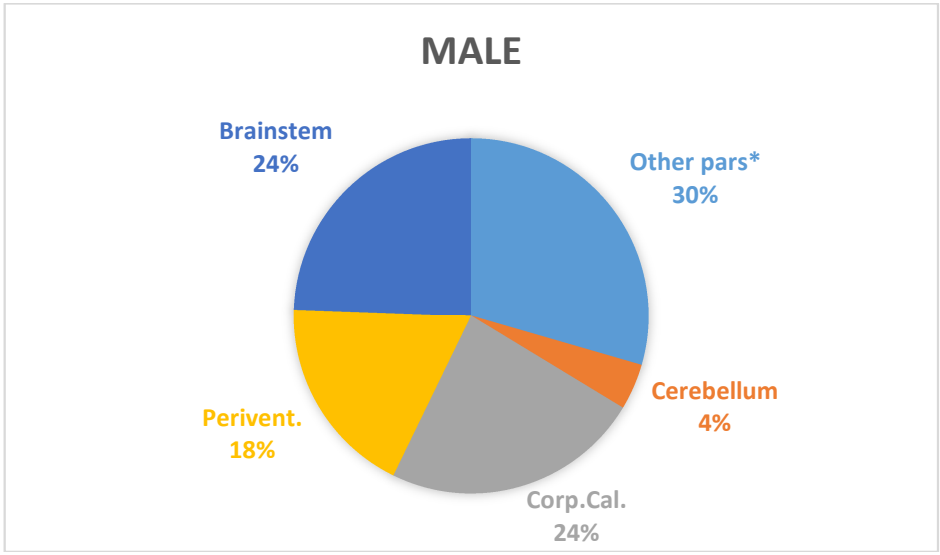
RESULTS



**: centrum semiovale and juxtacortical and subcortical white matter except the periventricular area*

Figure 1: anatomical distribution of MS plaques in Brain MRI





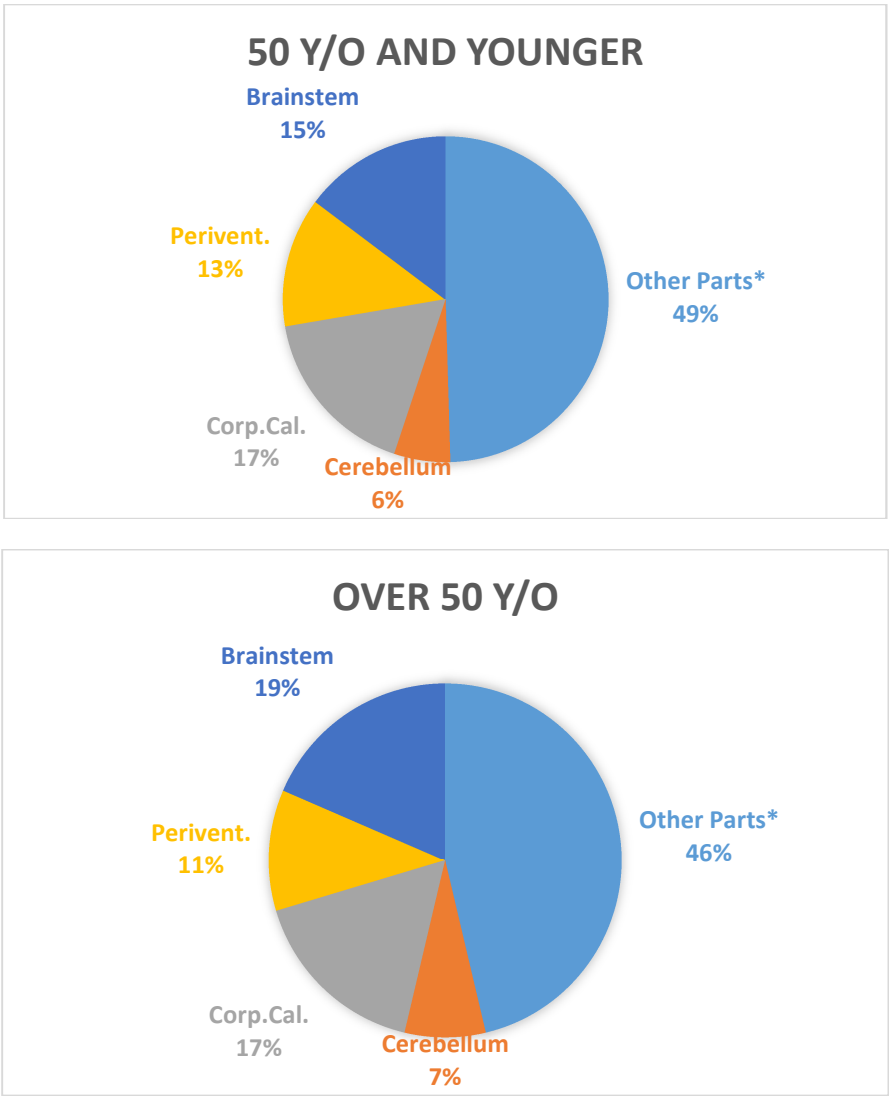
**: centrum semiovale and juxtacortical and subcortical white matter except the periventricular area*

Figure 2: anatomical distribution of brain plaques based on Sex

Table 1: p-value of anatomical distribution of brain plaques based on Sex

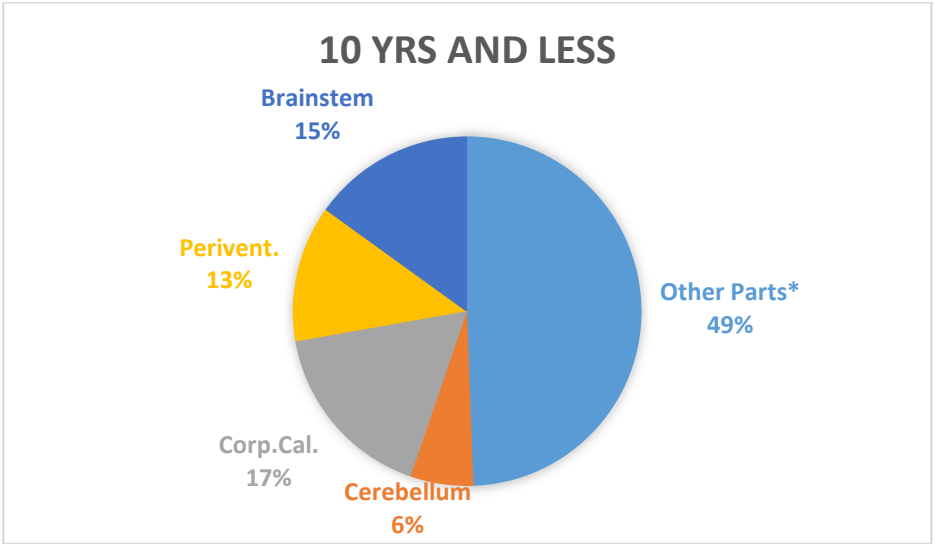
Region of Brain		Sex	P-Value
Brain Stem	*Pons*	F	.11
		M	.27
	Midbrain	F	.000
		M	.003
Cerebellum		F	.637
		M	.583
Corpus Callosum		F	.000
		M	.000
Periventricular		F	.000
		M	.000
*Other Parts**		F	.000
		M	.000

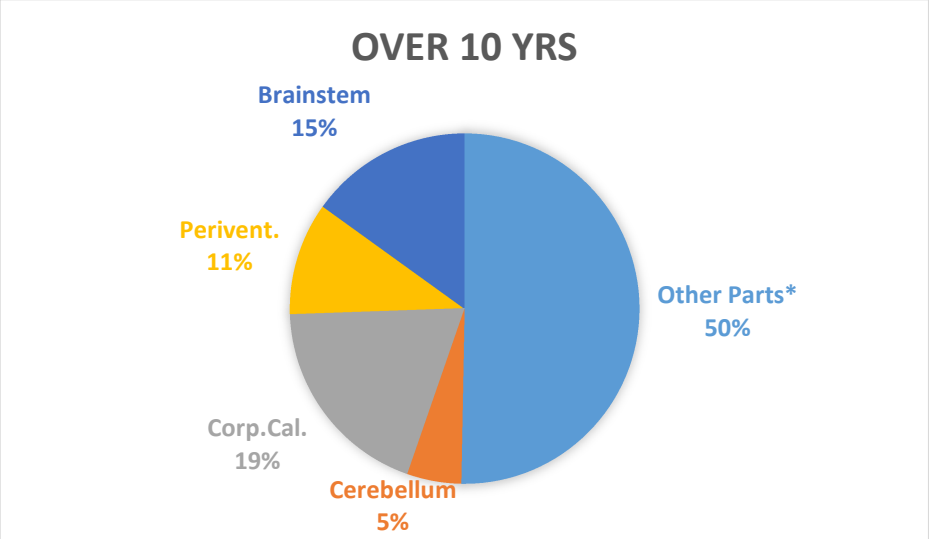
**: centrum semiovale and juxtacortical and subcortical white matter except the periventricular area*



**: centrum semiovale and juxtacortical and subcortical white matter except the periventricular area*

Figure 3: anatomical distribution of brain plaques based on age





**: centrum semiovale and juxtacortical and subcortical white matter except the periventricular area*

Figure 4: anatomical distribution of brain plaques based on duration of disease since diagnosis by neurologist

DISCUSSION AND CONCLUSION

During 3 months, 126 patients were entered into the study that 90 ones were females (71%) and 36 ones were males (29%). The mean age of the patients was 35.88±10.02 years old and the average of duration of disease in the patients was 5.66 ± 6.43 years.

During the T2W-MRI study of the patients' brain, 683 plaques were identified. The average number of the identified plaques in a single patient was 5.42±1.76. FLAIR imaging revealed 804 plaques in the study of patient' brain, the average number of the identified plaques in a single patient was 6.38±1.80. According to the previous studies (2), it seems that the in patients with MS, FLAIR has the ability to identify more plaques.For this reason, we will refer to the data of FLAIR as the reference in this study. The distribution of plaques in the Brain MRI of MS patients is : 15.59% in corpus callosum, 12.82% in brainstem, 11.44% in periventricular, 6.16% in cerebellum and 53.96% in other parts of white matter except the periventricular areas (centrum semiovale + juxta-cortical+subcortical) (Figure 1). In a study (24) carried out on 30 patients with MS, the most common area is periventricular (56%) and the distribution of the plaques in other parts of the brain is: Corpus callosum 6.7%, cerebrum 1.7% and other parts of white matter except the periventricular areas(centrum semiovale + subcortical + juxta-cortical) 32%; in another study (25) carried out on 84 patients with MS, the distribution of plaques in the different parts of the brain is as following: The white matter of the brain except the periventricular areas: 47%, periventricular 9.86%, corpus callosum 13.43%, cerebrum 5.31% The results of our study are similar to the results of the last study .

This study has been carried out in Shiraz City (next to Kerman province) and similarity of climatic conditions in both cities may has caused similar statistical results. But the results of the first study on Tabriz patients in northwest of Iran is completely different from ours because of two cities' complete climatic differences. Another reason is that in the first study, only 30 patients are evaluated and the little number of the samples may be subjected to the reduction of the statistical results accuracy.

In our study, in female Brain MRI, the anatomical distribution of plaques is as following:
Corpus callosum 14.22%, periventricular 10.08%, cerebellum 6.52%, brainstem 10.81% and other areas of the white matter except the periventricular area(centrum semiovale and subcortical and juxtacortical) 58.36%.
In the brain MRI of males, the anatomical distribution of the plaques is as following: Corpus callosum 23.35%, periventricular 18.19%, cerebellum 4.15%, brainstem 24.21% and other areas of the white matter except periventricular areas (centrum semiovale and subcortical and juxtacortical) 29.22%.

In both genders, the most common location of MS plaques in the Brain is the white matter except periventricular area and the rarest area is cerebellum. In our study, there was seen a significant relationship (p-value < 0.05) between the sex and anatomical distribution of MS plaques in the Brain. But, the cerebellum and the pons are exceptions and there is not seen any relationship between the plaque distribution and the sex in the cerebellum and the pons (Figure 3 and table 1). In a study (25) carried out over 84 patients with MS, 60 females and 24 males have

been evaluated regarding to the distribution of CNS plaques that the obtained results of the study showed that the relationship between the sex and the distribution of MS plaques in Brain MRI Images is significant. Also, it should be noted that the obtained results of our study showed that the percent of the plaques' occurrence in the Brainstem in males is two times higher than females. Also, in this study, the age is considered 50 years old to investigate the anatomical distribution of plaques. Among 126 patients entered into the study, 8 people are older than 50 years old and 118 ones are 50 years old or younger than 50 years. Due to the results of the statistical analysis, there is not observed a significant relationship between the age and anatomical distribution of MS plaques (Figure 3). In 2013 a study led by Bove et al (26) and published in BMC Neurology Magazine, There was no interaction between age and sex suggestive of an effect of reproductive aging on clinical or radiologic progression. It should be mentioned that in the related study the cerebral atrophy is evaluated as the radiological variance and the plaques distribution of MS in Brain MRI has not been evaluated between both groups .Also in this study, it is said that more studies is required in this field. In this study, duration of disease since the definite diagnosis of MS by neurologist is considered 10 years that among these 126 patients with MS, 16 people had duration of disease of higher than 10 years and 110 ones had 10 or less years of duration of MS. Due to the statistical analysis on the obtained data, there is not observed any significant relationship between the anatomical distribution of MS plaques and the duration of disease (Figure 4) but as in this study, no contrast is applied, active plaques are not evaluated and maybe there is a difference between the distribution of active MS plaques in patients with different duration of disease .so, this can be a subject for a new study. Also, in a cross sectional study (27), different patterns of phase change were identified in patients with different duration of disease. Hence, there are some differences regarding to the behavioral features of MS plaques in patients with different duration of disease but based on the results of our study, there is not observed any difference between the anatomical distributions of MS plaques in Brain MRI in patients with different duration of disease.

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