Secondary-progressive form of multiple sclerosis: MRI changes versus clinical status

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Submitted: 2008-07-17 Accepted: 2008-07-25 Published online: 2008-08-30

Key words: **MRI; demyelinating autoimmune diseases; multiple sclerosis, relapsing-remitting; multiple sclerosis, chronic progressive; brain atrophy**

Neuroendocrinol Lett 2008; **29**(4):461–466 **PMID:** 18766142 NEL290408A14 © 2008 Neuroendocrinology Letters • **www.nel.edu**

Abstract

OBJECTIVES: To monitor the interaction between the clinical manifestation of the secondary progressive form of multiple sclerosis (SPMS) expressed in the Expanded Disability Status Scale (EDSS) and abnormal findings in magnetic resonance imaging (MRI) of the brain. To compare a time line of brain atrophy in patients with SPMS, patients with relapsing-remitting multiple sclerosis (RRMS) and the healthy population. **METHODS**: Brain atrophy, volume of increased signal lesions on Fluid Attenuated Inversion Recovery Sequence (FLAIR) sequence (s.c.lesion load) and decreased signal lesions on T1 weighted sequence (s.c. black holes) were measured semi-automatically and correlated with EDSS in 12 patients. Further, we compared a time line of brain parenchyma fraction (BPF) loss in patients with SPMS, patients with RRMS and the healthy population. **RESULTS**: In patients with SPMS, no statistical correlation was found between lesion load in FLAIR and EDSS and there was also no significant statistical correlation (p=0.1134) between the volume of "black holes" and EDSS. However, we did confirm a significant correlation between increase in brain atrophy and clinical status (p=0.0093). Comparison of patients with SPMS or RRMS and the healthy population revealed that brain atrophy progressed most rapidly in patients with SPMS. **CONCLUSIONS**: The presence of a statistically significant difference in BPF loss between patients with SPMS or RRMS and the healthy population merits further study despite the small size of our sample. We postulate that the measurement of brain atrophy could be helpful in determining the transition of RRMS to SPMS and thereby predict the progression of the disease in the future.

INTRODUCTION:

Secondary progressive form of multiple sclerosis (SPMS) is characterized by a steady progression of clinical neurological damage with or without superimposed relapses and minor remissions and plateaus. Patients who develop SPMS will have previously experienced a period of RRMS, the majority of patients with RRMS will go on to develop SPMS with approximately 50% developing SPMS after 10 years. It remains unknown whether the relapsing and progressive phases of MS differ qualitatively. The pathogenesis of SPMS is poorly understood. Immunosuppressive therapies, which are capable of reducing or stopping clinical relapses and suppressing MR activity, generally do not stop disease progression (Giovannoni, 2004).

ORIGINAL ARTICLE

Abbreviations:
EDSS – Expanded Disability Status Scale
SPMS – Secondary progressive form of multiple sclerosis
RRMS – Relapsing-remitting multiple sclerosis
BPF – Brain parenchyma fraction
FLAIR – Fluid Attenuated Inversion Recovery Sequence

Magnetic Resonance Imaging (MRI) is very sensitive in the detection of pathological changes in the brain of patients with MS, but there is often a discrepancy between MRI findings and the patient's clinical status. The goal of the study was to monitor the interaction between the clinical manifestation of the secondary progressive form of multiple sclerosis expressed in EDSS and abnormal findings on brain MRI. The parameters under investigation included brain atrophy, volume of increased signal lesions on FLAIR sequence (s.c. lesion load) and decreased signal lesions on T1 weighted sequence (s.c. black holes).

Based on clinical status alone, it is difficult to precisely establish when RRMS converts to SPMS although it is clearly important for appropriate treatment. In the present study, we have compared the progression of brain atrophy over the course of 24 months in patients with SPMS, patients with RRMS and the healthy population with the aim of finding significant difference between these groups that could aid to differentiation between RRMS and SPMS based upon MRI findings.

MATERIAL AND METHODS:

Twelve patients diagnosed with SPMS were included in this study, nine men, three women, age range 32 to 54, average age 45.25 (Table 1).

Once a year the evaluation of the clinical status of the patient expressed in EDSS was performed, usually at the time of MRI examination. The EDSS screening occurred in an interval 10 days before to 10 days after the MRI examination.

Table 1. Patients with SPMS Included in the Study

Patient and Gender	Year of Birth	Year of MS Diagnosis	Year 1	Year 2	Year 3
1F	1947	1972	3	3	4
2M	1959	1986	6.5	6.5	6.5
3M	1957	1984	4	4.5	4.5
4M	1967	1995	5	5.5	6
5M	1948	1989	5	6	6.5
6M	1956	1980	4.5	5.5	6
7M	1950	1970	7	7	7
8F	1954	1977	4	4	4
9M	1968	1993	5.5	5.5	6
10M	1955	1992	5	6	6
11M	1953	1980	4.5	5.5	6.5
12F	1955	1975	3.5	4	4.5

As shown in Table 1, the EDSS of the patients in our study ranged from a high of seven to a low of three. During the timecourse of our investigation the average EDSS increased from 4.79 to 5.63.

All patients underwent a MRI examination every 12 months for 3 years. The same examination protocol was used for all patients. The examination protocol consisted of FLAIR (transversal scans, TIR, TR 11000, TE 140) and T1W (transversal scans, SE, TR 536, TE 14). Utilizing a special program developed in our Institution (Vaneckova *et al*, 2002), the following parameters were evaluated during each MRI examination:

1. Brain tissue volume (brain atrophy status)
2. Lesion load in FLAIR sequence.
3. Volume of "black holes" (volume of pathological lesions on T1W)

The first parameter evaluated was change in brain tissue volume. Each MRI examination was performed using the same protocol (from vertex to medulla oblongata). For volume-metric measurement brain atrophy and lesion load we used sequence FLAIR. Considering the fact that the absolute volume in cm^3 differs from patient to patient, it is not appropriate to look for a correlation between the absolute volume of brain tissue and EDSS. The relative change of brain tissue volume was measured to ascertain if there is a correlation with clinical status of the patient. The base value of brain tissue volume of each patient was assumed to be 100 percent.

We defined the brain tissue as a tissue with signal level intensity of 4000 and the MS plaque as a lesion with signal level intensity of 9000 (Figure 1). The volume of lesions was then calculated automatically.

For the volume-metric cblealculation of "black holes" we used the axial plane with the thickness of 6 mm. The decreased signal lesions on axial scans in T1W ("black holes") were semi-automatically marked (Figure 2). Then the volume of the "black holes" was automatically calculated for all three control studies. The results were correlated with the corresponding EDSS.

The final part of the study compared the development of brain atrophy among patients with SPMS, patients with RRMS and the healthy population. This comparison was possible thanks to our extensive patient database. We grouped all patients with MS (SPMS and RRMS) and compared them to non-MS (healthy) patients. The MRI sequences were identical in both groups. In the group of non-MS patients we used gender and age as parameters, for MS patients we added the length of time suffering from the disease; thus both groups were close to each other in age and gender.

Because the absolute value of brain volume is different in each patient, it was necessary to first calculate the value of the brain parenchyma fraction (BPF) following each examination. The BPF is calculated as the proportion of brain tissue to the whole brain volume, including cerebro-spinal fluid spaces. By calculating BPF, we obtain comparable data for each set of subjects that had

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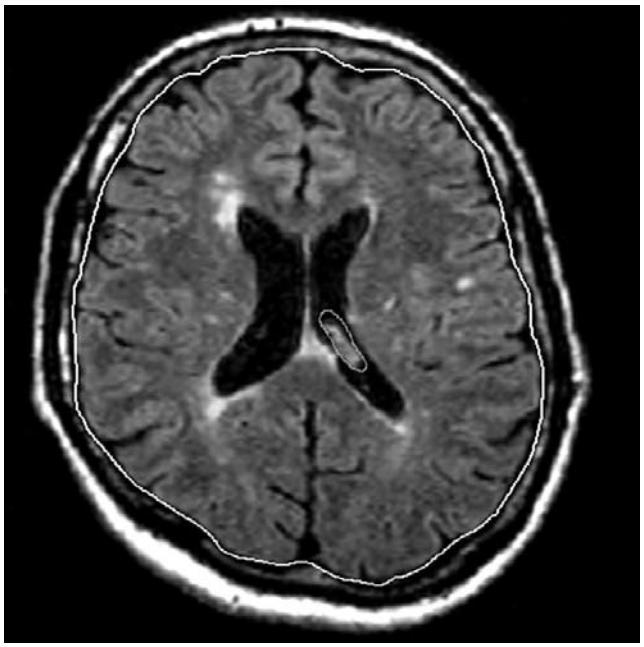

Figure 1. Patient with SPMS, transversal scan in FLAIR in first year of the study. Brain tissue and flow artifacts in lateral ventricles are demarcated.

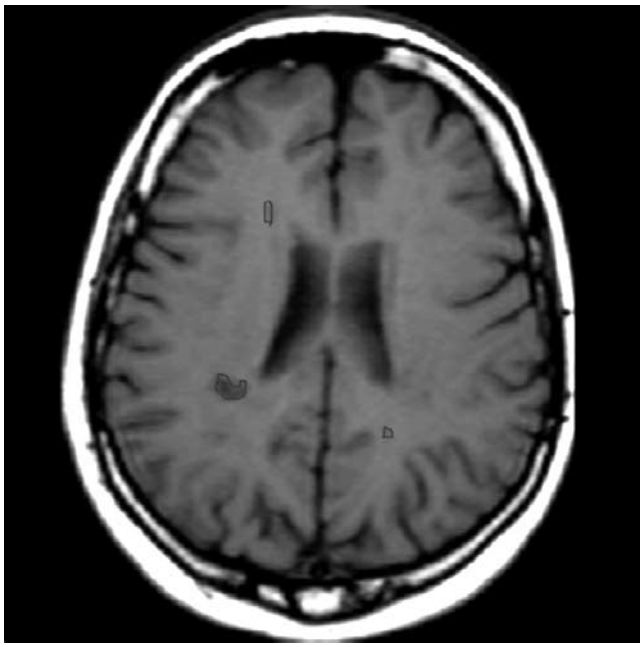

Figure 2. Patient with SPMS, transversal scan in T1WI. Hypointense lesions (black holes) are demarcated.

been grouped together, which allows us to study the development of brain atrophy over time in each of the three groups (RRMS, SPMS and healthy patients). The change in BPF for each group was calculated over the course of 24 months.

The t-test was used for statistical evaluation.

The authors confirm that the procedures carried out on the patients studied were in accordance with the ethical standards of the World Medical Association (Declaration of Helsinki). In addition, all of the authors ensured that their work complies with local ethical committee standards and the subjects gave their informed consent to participate. Publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out. The authors and authors' institutions have no conflicts of interest.

RESULTS:

In patients with SPMS, we found a statistically significant correlation (p=0.0093) between EDSS scores and brain atrophy (Figure 3, Table 2)

However, there was no statistically significant correlation found between the volume of increased signal lesions in FLAIR (Table 3) and EDSS (p=0.4726). The relatively wide variation in measurements from one year of the study to the next year in some patients could be explained by changes in the inflammatory activity of the lesions.

We next examined the possible correlation between EDSS and "black holes." Table 4 displays the volume of decreased signal lesions in cm^3 in T1 weighted sequences in patients with SPMS.

No statistically significant correlation between absolute volume of decreased signal lesions in T1WI and EDSS was found (Figure 4), however, there seems to be a trend (p=0.1134) to this correlation. A larger set of data is necessary to definitively confirm the existence of such a trend.

In the final phase of our study, we compared brain atrophy development in patients with different forms of MS to members of the healthy population.

Table 5. The differences in BPF among patients with SPMS (patients 1–11 – one patient dropped out of the study), patients with the RRMS (patients 12–22) and healthy patients (patients 23–33).

The difference is shown in bold type in the table. BPF 1 indicates the BPF measurement at the beginning of the study while BPF 2 indicates the measurement at the end of the study.

There is a statistically significant difference between all three groups – healthy population, patients with SPMS, and patients with RRMS – in brain atrophy development (Figure 5). The development of brain atrophy is significantly faster and more pronounced in patients with MS compared to the control group of healthy patients. Among patients suffering from MS, brain atrophy progressed more rapidly in patients with SPMS than in patients with RRMS. For comparison the level of p in the increase of brain atrophy in patients with SPMS compared to the healthy population is 2.99022×10^5. Comparing the healthy population to patients with RRMS yields p=0.03006748, while in a comparison of patients with SPMS and RRMS, p=0.001122453. The fact that patients with SPMS had higher BPF levels than patients with RRMS was not statistically significant (p=0.39).

Table 2. Volume of Brain Tissue at or Above Signal Intensity of 4,000

Patient	Measure	Year 1	Year 2	Year 3
1	cm^3	993.81	987.97	980.18
	%	100	99.41	98.63
2	cm^3	1385.35	1366.47	1343.31
	%	100	98.64	96.97
3	cm^3	1147.12	1138.64	1130.39
	%	100	99.26	98.54
4	cm^3	1356.93	1336.66	1305.97
	%	100	98.51	96.24
5	cm^3	1319.52	1291.48	1281.38
	%	100	97.87	97.11
6	cm^3	1150.95	1091.86	1074.07
	%	100	97.84	96.25
7	cm^3	1183.95	1173.10	1143.25
	%	100	99.20	96.85
8	cm^3	1198.04	1169.80	1169.90
	%	100	97.64	97.65
9	cm^3	1280.66	1278.14	1249.16
	%	100	99.8	97.54
10	cm^3	1258.61	1237.56	1243.75
	%	100	98.33	98.82
11	cm^3	1339.65	1299.30	1263.87
	%	100	96.99	94.34
12	cm^3	1199.84	1173.07	1177.53
	%	100	97.77	98.14

Table 3. Volume of increased signal lesions in FLAIR at or above signal intensity of 9,000.

Patient	Measure	Year 1	Year 2	Year 3
1	cm^3	12.48	11.37	12.21
	%	100	91.11	97.84
2	cm^3	7.97	7.41	8.21
	%	100	92.97	103.01
3	cm^3	3.60	4.97	6.00
	%	100	138.44	167.13
4	cm^3	5.67	5.34	6.31
	%	100	94.18	111.29
5	cm^3	1.28	1.45	1.79
	%	100	113.28	139.84
6	cm^3	23.90	21.36	26.80
	%	100	89.37	112.13
7	cm^3	22.24	21.94	24.38
	%	100	98.65	109.62
8	cm^3	7.39	11.63	10.62
	%	100	122.92	116.82
9	cm^3	30.84	22.26	23.94
	%	100	72.18	77.63
10	cm^3	3.66	4.12	3.15
	%	100	112.57	86.07
11	cm^3	29.30	26.22	27.69
	%	100	84.49	94.51
12	cm^3	2.03	2.40	2.59
	%	100	118.23	127.59

Table 5. The differences in BPF among patients with SPMS (patients 1-11 - one patient dropped out of the study), patients with the RRMS (patients 12-22) and healthy patients (patients 23-33).

Patient	BPF 1	BPF 2	Difference	Patient	BPF 1	BPF 2	Difference	Patient	BPF 1	BPF 2	Difference
1	82.24	77.76	**-4.48**	12	79.90	78.97	**-0.93**	23	86.51	86.96	**0.44**
2	83.64	81.30	**-2.34**	13	85.60	84.97	**-0.62**	24	87.62	88.06	**0.43**
3	85.01	82.59	**-2.41**	14	82.79	80.50	**-2.28**	25	87.29	87.66	**0.36**
4	85.31	82.26	**-3.05**	15	86.63	86.13	**-0.49**	26	84.95	84.76	**-0.18**
5	84.83	83.78	**-1.05**	16	81.27	80.67	**-0.59**	27	85.79	85.42	**-0.36**
6	84.07	80.32	**-3.74**	17	86.56	85.35	**-1.20**	28	84.34	83.75	**-0.58**
7	84.06	82.34	**-1.72**	18	86.09	84.92	**-1.17**	29	83.88	82.99	**-0.88**
8	83.66	82.58	**-1.07**	19	84.36	83.56	**-0.79**	30	86.35	86.53	**0.17**
9	84.91	82.92	**-1.98**	20	84.97	85.70	**0.73**	31	83.85	83.63	**-0.22**
10	84.13	82.20	**-1.92**	21	83.22	82.05	**-1.17**	32	85.24	84.84	**-0.40**
11	86.13	84.49	**-1.64**	22	77.72	77.64	**-0.08**	33	83.40	82.92	**-0.47**

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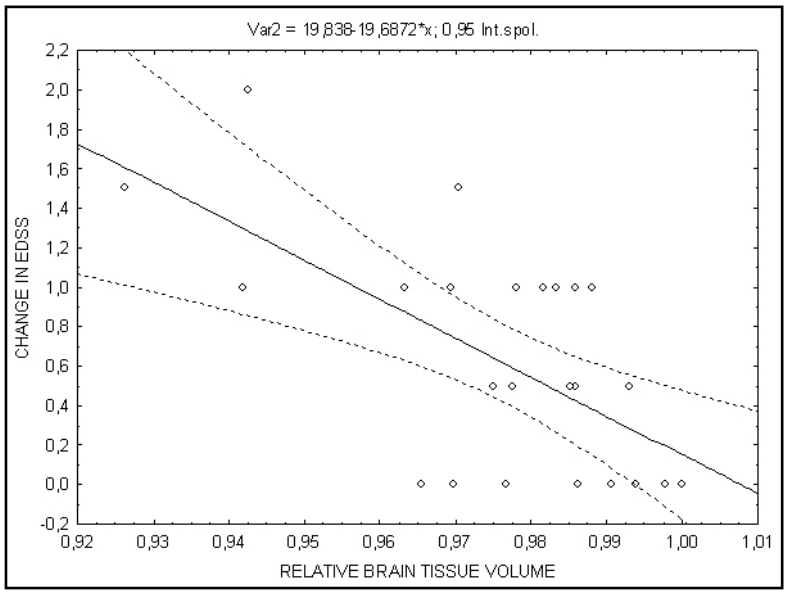

Figure 3. Correlation between relative brain tissue volume and the change in EDSS.

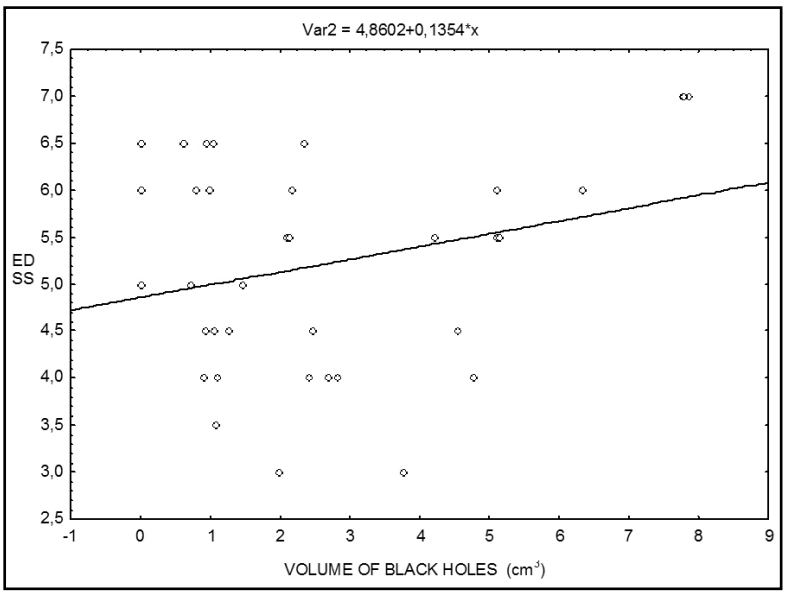

Figure 4. Correlation between EDSS levels and the volume of "black holes."

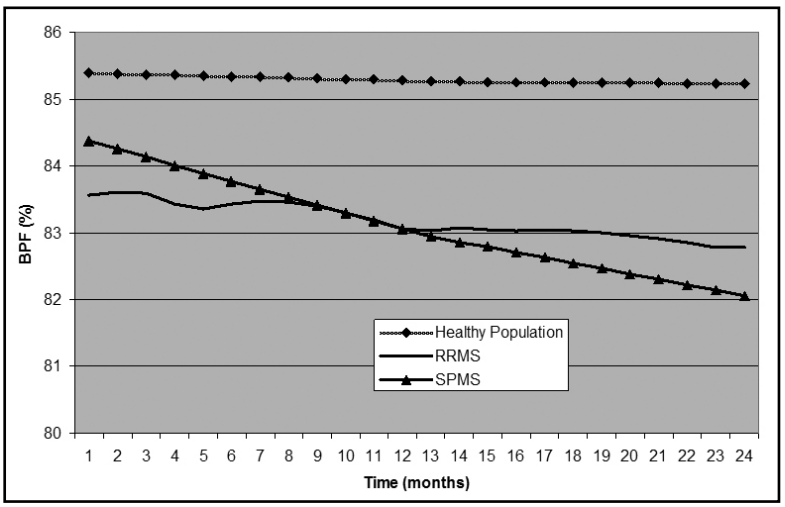

Figure 5. The graph shows the differences in brain atrophy development in all three groups. The points on the graph indicate BPF changes over time. For each time period, the average BPF value is plotted for each of the three groups

Table 4. Volume of decreased signal lesions in cm^3 in T1weighted sequence in patients with SPMS.

Patient	Year 1	Year 2	Year 3
1	1.99	3.76	4.76
2	0.62	1.03	0.94
3	0.90	0.93	1.27
4	1.47	2.14	2.16
5	0.00	0.00	0.00
6	4.53	5.10	6.34
7	7.85	7.76	7.78
8	2.41	2.68	2.81
9	4.21	5.13	5.10
10	0.70	0.99	0.80
11	2.46	2.10	2.34
12	1.08	1.10	1.05

DISCUSSION:

The sta\tistical correlation between the volumetric results and EDSS in our study confirmed the strong association between progression of brain atrophy in patients with SPMS and changes in EDSS. Similar findings have been described by other authors. Dastidar *et al.* (1999) found a significant association between neurological deficiencies (as expressed by EDSS) and brain atrophy in RRMS patients. Bakshi *et al.* (2005a) came to the conclusion that CNS atrophy shows significant associations with neurological manifestation of MS and that the atrophy appears to be a risk factor for disease progression independent of lesion load. Brain atrophy was particularly well correlated with neuropsychological impairment. Fisher *et al.* (2002) concluded in clinical trials that changes in brain atrophy, expressed by BPF changes, correlated with changes in EDSS. Patients with higher levels of atrophy in the first two years of their study presented higher levels of neurological deficiency during the eight years of the follow up. Fisher also concluded that changes in BPF during the first two years were a better predictor of neurological deficiency than changes in lesion load in T1 and T2 weighted images and Gadolinium-enhanced sequences.

While comparing the progression of brain atrophy in patients with SPMS, patients with RRMS and the healthy population, we found the fastest and comparatively greatest progression of atrophy in patients with SPMS in comparison to patients with RRMS; progression of atrophy was the most limited and slowest in the healthy population. Recent literature (Prinster *et al*., 2006; Tedeschi *et al*., 2005) also confirms more significant atrophic changes in patients with SPMS then in patients with RRMS. We assume that the acceleration of BPF loss could help to determine the transition of RRMS to SPMS and thereby be the indicator and predictor of the future progression of the disease. In our department, we routinely include volumetry of brain tissue in the standard examination protocol of patients with MS.

Presently it is accepted that brain atrophy along with "black holes" reflect more accurately the neurodegenerative and destructive components of MS disease process and that "black holes" represent areas with severe demyelinization, axonal loss and destruction of the brain matrix (Zivadinov *et al*., 2004; Bakshi *et al*., 2005b). Sailer *et al*. (2001) found significant correlation between changes in the volume of "black holes" and brain atrophy and pointed out parallel changes in T1 weighted MRI images and changes in EDSS. Naismith *et al*. (2005) confirmed the correlation between the volume of "black holes" and neurological impairment in patients with SPMS. Statistical evaluation of changes in "black holes" volume and EDSS in our study showed a tendency that would need to be confirmed with more data. However, our study confirmed an additional characteristic of "black holes" – that "black holes" change with time. In some of our subjects the volume of "black holes" was smaller in second year of the study than in the first year. Zivadinov *et al*. (2005) concluded that most newly formed black holes will revert to iso-intensity within a few months because of remyelination and the resolution of oedema.

The changes in the volume of increased signal lesions on T2 weighted images do not correlate with changes in EDSS. This finding can be explained by the non-specificity of changes in FLAIR sequence which can not distinguish between pathological substrata like inflammation, oedema and demyelinization in increased signal lesions. The discrepancy between clinical status and MRI findings is called "clinical – MRI paradox" (Bakshi *et al*., 2005b; Zivadinov *et al*., 2005).

CONCLUSIONS:

While looking for a relationship between clinical status and MRI pathological findings in patients with SPMS, we found the strongest correlation between EDSS and brain atrophy. The progression of brain atrophy, expressed by brain parenchyma fraction (BPF) loss, is also significantly the fastest and comparatively the greatest in SPMS patients in comparison to RRMS patients and in comparison to healthy population. Although the number of patients in our study was limited, the presence of a statistically significant difference in BPF loss in all three groups encourages us to continue investigating this phenomenon in follow-up study with more patients. We postulate that an acceleration of BPF loss in RRMS patients could help to determine the transition to SPMS and thereby be an important correlate of disease progression.

Acknowledgement:
This study was supported by a research grant by from the Ministry of Health of Czech Republic (MZO/00064165 and MSMOO 21620849).

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