Medicina (Kaunas) 2012;48(9):437–41

Volumetric MRI Assessment of Brain and Spinal Cord in Finnish Twins Discordant for Multiple Sclerosis

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Key Words: *multiple sclerosis; twins; brain atrophy; heritability; white matter; magnetic resonance imaging; volumetry.*

Summary*. Background and Objective. Brain size, white matter hyperintensity, and the development of brain atrophy are known to be highly heritable. The decrease of brain volume starts from the very onset of multiple sclerosis and is 10-fold compared with normal aging. The aim of this study was to assess whether the brain and spinal cord volumes and the volume of white matter lesions differed between twins with multiple sclerosis and their asymptomatic co-twins.*

Material and Methods. A co-twin control method was used to evaluate whether the brain and spinal cord volumes differ between twins with multiple sclerosis and their co-twins. Nineteen twin pairs were studied neurologically, and the volumes of T1, T2, FLAIR, and gadolinium-enhanced lesions and those of the brain and the spinal cord were obtained by magnetic resonance imaging.

Results. Significant differences in the brain (P=0.064) or spinal cord (P=0.648) volumes were not detected. Four of the 7 monozygotic and 5 of the 12 dizygotic co-twins had focal brain white matter lesions, but none fulfilled the magnetic resonance imaging criteria of Barkhof. Spinal cord lesions were not seen in any of the co-twins.

Conclusions. The absence of a significant difference in the brain or spinal cord volume between the twins with multiple sclerosis and their co-twins supports the recent observation of brain size and the development of brain atrophy being highly heritable.

Introduction

Focal white matter lesions (WMLs) characterized by inflammation, demyelination, remyelination, edema, axonal damage, and gliosis are easily visible on brain MRI and are present in more than 90% of patients with clinically definite multiple sclerosis (MS) (1–4). Previously, 3 family and 3 twin studies have investigated the incidence of such lesions in clinically asymptomatic subjects with a genetic susceptibility to MS by using specific magnetic resonance imaging (MRI) criteria (5–10). According to these studies, MS-like lesions can be detected in 4%–10% of asymptomatic subjects having a first degree relative with MS. On the other hand, autopsy studies have revealed that the prevalence of MS-like brain WMLs in healthy subjects with no risk of MS is equivalent to the prevalence of MS in the general population of the United States (0.1% of the population) (11–13). In addition to focal WMLs, brain atrophy starts to develop in the majority of MS patients, often from the very onset of the disease (14–16). The annual decrease in the brain volume in healthy subjects is approximately 0.1%–0.3% (17, 18), whereas in MS patients, it is 0.6%–1.0% (18–20). According to the recent studies, brain size, white matter (WM) hyperintensity, and the development of brain atrophy are highly heritable (21–28).

A registry-based co-twin control method was used to evaluate the degree of brain atrophy in twins with MS and their asymptomatic co-twins. In order to evaluate the possibility of so-called subclinical MS in asymptomatic twins, the presence and volumes of focal WMLs were evaluated both in the brain and the spinal cord (SC), which is not known to be affected by aging (29).

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Material and Methods

Seven monozygotic (MZ) and 12 dizygotic (DZ) twin pairs discordant for MS, obtained from the Finnish Twin Cohort (30), participated in this study. All subjects provided written informed consent before the study entry. The study was approved by the Ethics Committee of Tampere University Hospital. The collection of the study population and verification of MS diagnosis have been described in detail previously (30). All subjects underwent a neurological examination by the same neurologist (H.K.). The diagnosis of MS was based on the McDonald's (2) criteria of clinically definite MS. All twins had remission at the time of the study. The clinical characteristics of the twins are shown in Tables 1, 2, and 3. Three twins with MS had a coexisting dis-

Table 1. Clinical Characteristics of the Twins With Multiple Sclerosis

Twins With MS (n=19)	Age Median (Range)	EDSS Median (Range)	Disease Duration, Years Median (Range)	RR MS (n)	SP MS (n)	PP MS (n)	Patients With Disease Modifying Therapy (n)
MZ (n=7)	51 (30–66)	5.0 (2.0–7.0)	11 (1–23)	3	4	0	2
DZ (n=12)	52 (39–58)	2.5 (1.0–8.0)	16.5 (4–25)	5	4	3	5

MZ, monozygotic; DZ, dizygotic; RR, relapsing-remitting; SP, secondary progressive; PP, primary progressive; MS, multiple sclerosis; EDSS, expanded disability status scale; disease duration, time from diagnosis of MS.

Table 2. Characteristics and the MRI Results of the Twin Pairs

Twin Pairs	Age, Years	Sex	Barkhof's Criteria	Zygosity	Disease Type	EDSS	Disease Duration, Years	T2 Volume cm^3	T1 Volume cm^3	Flair Volume cm^3	Brain Volume cm^3	SC Volume cm^3
1	51	F	neg	MZ		0	0	0.47	0.37	1.3	1115.52	0.3094
1-MS	51	F	pos	MZ	SP	1.5	11	2.2	24.77	12.1	1076.14	0.2522
2	42	M	neg	MZ		0	0	0.04	0.04	1.01	1136.57	0.2388
2-MS	42	M	pos	MZ	SP	6.5	22	10.26	3.17	38.99	1035.89	0.2611
3	30	F	neg	MZ		0	0	0	0	0	1297.49	0.3381
3-MS	30	F	pos	MZ	RR	5	5	9.38	5.27	22.3	1164.98	0.2891
4	45	F	neg	MZ		0	0	0	0	0	1182.47	0.2282
4-MS	45	F	neg	MZ	RR	4	1	0.07	0.09	0.62	1091.2	0.3194
5	52	M	neg	MZ		0	0	0	0	0	1363.93	0.3196
5-MS	52	M	pos	MZ	SP	6.5	23	15.82	7.36	39.95	1226.47	0.3348
6	51	F	neg	MZ		0	0	0.31	0	2.48	1162.45	0.2875
6-MS	51	F	pos	MZ	RR	4.5	3	6.59	3.88	19.4	1081.45	0.2406
7	66	M	neg	MZ		0	0	0	0.08	0.22	1104	0.2773
7-MS	66	M	pos	MZ	SP	6.5	11	1.49	1.3	6.42	1101.4	0.2517
8	56	F	neg	DZ		0	0	0	0	0	1216.69	0.2204
8-MS	56	F	pos	DZ	SP	2.5	20	2.27	1.04	11.69	1081.91	0.2251
9	41	F	neg	DZ		0	0	0	0	0	1183.36	0.2834
9-MS	41	F	pos	DZ	RR	1.5	25	3.87	2.37	16.34	1140.7	0.2591
10	39	F	neg	DZ		0	0	0	0	0	1053.39	0.3009
10-MS	39	F	pos	DZ	RR	1	22	2.7	0.46	9.42	1092.46	0.3302
11	54	M	neg	DZ		0	0	0.17	0	0.63	1295.33	0.2699
11-MS	54	F	neg	DZ	RR	2.5	6	0.08	0	0.97	1062.28	0.2756
12	54	F	neg	DZ		0	0	0.07	0	0.31	1104.65	0.2711
12-MS	54	M	pos	DZ	SP	6	13	0.14	0	0.94	1388.85	0.2380
13	58	F	neg	DZ		0	0	0.37	0	1.21	1046.62	0.2967
13-MS	58	M	pos	DZ	PP	8	13	24.68	15.88	68.02	935.06	0.2600
14	51	M	neg	DZ		0	0	0	0	0	1252.83	0.3332
14-MS	51	F	neg	DZ	SP	3.5	17	0.02	0.07	0	1161.32	0.3335
15	53	M	neg	DZ		0	0	0	0	0	1024.53	0.3333
15-MS	53	F	neg	DZ	SP	4	12	1.34	0.79	5.91	1168.78	0.2669
16	40	F	neg	DZ		0	0	0	0	0	1028.48	0.2582
16-MS	40	M	pos	DZ	PP	6.5	4	6.23	7.25	11.43	1105.43	0.2319
17	49	F	neg	DZ		0	0	0	0	0	1140.25	0.3276
17-MS	49	F	pos	DZ	RR	1	16	2.37	0.74	7.59	1007.53	0.2901
18	56	F	neg	DZ		0	0	0.01	0	0.43	1116.7	0.3399
18-MS	56	F	pos	DZ	PP	2.5	23	0.65	0.86	2.74	973.52	0.2524
19	51	F	neg	DZ		0	0	0.09	0	0.23	1138.19	0.3285
19-MS	51	F	neg	DZ	RR	1	20	0.19	0.07	0.37	1235	0.3320

F, female; M, male; DZ, dizygotic; MZ, monozygotic; RR, relapsing-remitting; SP, secondary progressive; PP, primary progressive; EDSS, expanded disability status scale; SC, spinal cord.

ease: 1 twin had atrial fibrillation, the second had eosinophilic pneumonia, and the third suffered from asthma. Nine of the co-twins had also some chronic diseases, with hypertension, psoriasis, and asthma being the most common (each in 2 subjects). The diseases of the co-twins presenting with WMLs are shown in Table 3. The individual study results were provided to all subjects after the MRI evaluation.

Magnetic Resonance Imaging. All twins underwent 1.5-tesla (T) MRI of the brain and the SC. The

Table 3. Characteristics of the Asymptomatic Co-Twins With White Matter Lesions

Twin No.	Zygosity	Sex	Age, years	Concomitant Diseases	Alcohol*	Smoking	T1 cm^3	T2 cm^3	Flair cm^3	Brain cm^3	SC cm^3
1	MZ	F	51	Schizophrenia	No	No	0.37	0.47	1.3	1115.52	0.3094
2	MZ	M	42	None	Yes	No	0.04	0.04	1.01	1136.57	0.2388
6	MZ	F	51	None	No	No	0	0.31	2.48	1162.45	0.2875
7	MZ	M	66	Coronary heart disease	No	No	0.08	0	0.22	1104.00	0.2773
11	DZ	M	54	Asthma	No	Yes	0	0.17	0.63	1295.33	0.2699
12	DZ	F	54	Hypertension	No	No	0	0.07	0.31	1104.65	0.2711
13	DZ	F	58	Hypertension	No	No	0	0.37	1.21	1046.62	0.2967
18	DZ	F	56	Arthrosis and hypothyreosis	No	No	0	0.01	0.43	1116.70	0.3399
19	DZ	F	51	None	No	No	0	0.09	0.23	1138.19	0.3285

MZ, monozygotic; DZ, dizygotic; F, female; M, male.
*More than 24 cl/day.

MRI evaluation was undertaken blindly from coded pictures by an experienced neuroradiologist (P.D.). Examinations were performed using the same scanner (GE Signa Horizon LX, Wisconsin, USA). Axial 3-dimensional (3D) T2 fast spin echo (FSE), T1 3D axial spoiled gradient echo (SPGR), and FLAIR sequences were used to perform volumetric analyses of plaques and brain volumes. The sagittal 3D T2 FSE sequence was used to perform analyses of the SC and spinal canal volumes. Good head repositioning was controlled using the same head coil, the same anatomic locations, and the same pack of images in different MRI sequences. The SC was scanned by separating it into the upper (cervico-thoracic) and lower (thoraco-lumbar) parts.

Image Analysis of Plaques and Atrophy. T2 hyperintense plaques were analyzed from 3D T2 FSE images, T1 hypointense plaques from 3D T1 SPGR images, and FLAIR lesions from FLAIR images. Brain volumes were analyzed from 3D T1 FSE images. First, the total intracranial volume was measured adding both the total cerebral volume and the total cerebrospinal fluid. The ratio of the total cerebral volume to the total intracranial volume was used as a marker of cerebral atrophy. The SC and spinal canal volumes were analyzed from sagittal 3D T2 FSE images, and the ratio of the SC volume to the spinal canal volume was used as a marker of SC atrophy. Since the FLAIR sequence was not 3D in nature, the lesion volumes in the gap between 2 slices were estimated by multiplying the average cross-sectional area of the plaque structures by the gap thickness. The total number and location of the MRI lesions were analyzed by using the criteria of Barkhof (31).

Statistical data analysis was performed using the SPSS for Windows, version 14.0.2. *P* values less than 0.05 were considered statistically significant. Due to the skewed distributions, continuous variables were expressed as medians and ranges, and differences between asymptomatic twins and twins with MS were tested by paired exact signed test.

Results

No significant differences were found in brain (P=0.064) or SC (P=0.648) volumes between the twins with MS and their co-twins (Table 4). All 19 twins with MS had focal brain WMLs, and 14 of them (74%) fulfilled the MRI criteria of Barkhof (Table 2). Nine of the 19 (4/7 MZ and 5/12 DZ) co-twins had focal brain WMLs seen on T1, T2, or FLAIR images, but the MRI criteria of Barkhof were not fulfilled in any of these subjects (Table 2). All but one of the co-twins presenting with WMLs was over 50 years. The remaining one had excessive alcohol consumption as a risk factor for the development of WMLs. Of the 9 co-twins presenting with WMLs, 7 had a chronic disease, and of the 10 co-twins with no WMLs, 2 had a chronic disease (asthma and hypertension). Three twins with MS had a SC lesion, but no such lesions were present among the co-twins (Table 2). The volumetric results of twins with MS and their co-twins are presented in Table 4. In the subgroup of co-twins with focal brain WML (n=9), the volumes of T1 (P=0.016), T2 (P=0.039), and FLAIR lesions (P=0.004) were significantly smaller than in the twins with MS (n=19).

Discussion

Even though the annual decrease in brain volume of MS patients is 10-fold compared with healthy people (18, 19), the brain size in a genetically homogenous patients' population such as the twins discordant for MS appeared to be without a

Table 4. Volumetric Results of the Twins With Multiple Sclerosis and Their Asymptomatic Co-Twins

	Asymptomatic Co-Twins (n=19)	Twins With MS (n=19)	*P*
T1, cm^3	0 (0–0.37)	1.04 (0–24.77)	<0.001
T2, cm^3	0 (0–0.47)	2.27 (0.02–24.68)	<0.001
FLAIR, cm^3	0 (0–2.48)	9.42 (0–68.02)	<0.001
Brain, cm^3	1138 (1025–1364)	1092 (935–1389)	0.064
SC, cm^3	0.30 (0.22–0.34)	0.26 (0.23–0.33)	0.648

Values are median (range).
SC, spinal cord; MS, multiple sclerosis.

marked difference. Our findings may be explained by a recent observation indicating that the brain size is a highly heritable parameter, and the development of generalized brain atrophy may be genetically regulated (21, 22). The genetic contribution to the volume of the lateral ventricles has been shown to increase with age, accounting for 75% of the variance after middle age (22). In addition to genes, twins share many environmental factors during the fetal life, childhood, and adolescence, such as nutrition, sunlight exposure (vitamin D), passive smoking by the parents, and various infections, some of which may also influence the brain size and the rate of atrophy making it difficult to detect a difference in brain size in diseased and asymptomatic subjects.

In MS, both gray and WM regions are affected by atrophy, but their pathogenesis differs (32). In WM, atrophy results mainly from the focal loss of myelin and axon density due to inflammation (32, 33), whereas gray matter atrophy is caused by direct axonal injury that predominates especially in secondary progressive MS (SPMS) (34). When adjusted to the baseline brain volume, overall brain atrophy develops throughout the course of MS at the rate, which is independent of the disease subtype (35). However, the mechanisms of atrophy in relapsing remitting MS (RRMS) and SPMS differ. Early in the disease process that is predominantly characterized by inflammatory activity, atrophy affects both white and gray matter, whereas on transition to the SPMS phase, atrophic changes of gray matter start to prevail (34). Since the median age of our twins was more than 50 years and the median duration of MS was more than 10 years, it is likely that both inflammatory and degenerative mechanisms have contributed to the development of loss in the brain volume. Even so, we could not detect a difference in brain volume between our groups, most likely because twins share both genes and environmental factors that may regulate the brain size and the rate of brain atrophy due to normal aging.

Radiological studies performed on MS patients have revealed a frequent involvement of SC even in the absence of any spinal symptoms or signs. When evaluating the clinical significance of WM lesions in the central nervous system (CNS) in asymptomatic subjects, MRI of the SC is especially valuable since the SC is not affected by aging (29). In the present study, we could not detect WMLs in the SC of the asymptomatic co-twins, though they were a frequent event in the brain, especially in subjects aged more than 50 years and with chronic diseases. However, the volume of these lesions was small, and none of the co-twins presenting with WMLs fulfilled the Barkhof's MRI criteria (31), indicating that they might be related to age and existing risk factors (Table 3) rather than so-called subclinical MS characterized by the presence of oligoclonal bands in cerebrospinal fluid and/or silent WMLs on brain MRI. Our results are in line with the findings of DeStefano and colleagues, who proposed that even though there is a genetic susceptibility to the development of brain WMLs in first-degree relatives of MS patients, they do not lead to widespread tissue damage and clinical MS disease (35). Due to the limited number of twins in this study, we cannot however exclude the possibility of subclinical MS in this genetically at risk population, even though our findings did not support the idea.

The relation between WMLs and brain atrophy has been found in various diseases including MS (36, 37) as well as in asymptomatic elderly people. Whether this is independent of shared vascular risk factors has yet to be shown (37). Since the common vascular risk factors including hypertension, hyperlipidemia, obesity, diabetes mellitus, and smoking have been found to be associated with both the development of WML and brain atrophy, it has been suggested that vascular mechanisms contribute to the progression of brain atrophy during aging (37–44). On the other hand, WM hyperintensity has been shown to be highly heritable, and therefore, a good genetic marker for brain aging even in subjects with the low prevalence of cerebrovascular brain injury (23). In the present study, no difference in brain volumes between twins with MS and co-twins was found even though there was a significant difference in WML volumes. This result supports the previous findings that the brain volume in twins is highly heritable (23, 24). It should be noted that our study was not designed to evaluate the association of WMLs and brain atrophy in twins with MS or their co-twins, and therefore, the study population is too small to make any such correlations.

Conclusions

The lack of a significant difference in the brain or spinal cord volumes between twins with multiple sclerosis and their co-twins is most likely to be explained by the recent observation showing the brain size and the development of brain atrophy being highly heritable.

Acknowledgments

The support for this study was provided by the Finnish Neurology Foundation, the Orion Research Foundation, and the Medical Research Fund of Tampere University Hospital.

Statement of Conflict of Interest

The authors state no conflict of interest.

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Received 28 May 2012, accepted 30 September 2012