Genetic and clinical risk factors for spasticity among people with MS

Smith KA,[1,2] Alfredsson L,[2,3] Piehl F,[2,4] Olsson T,[2,4] Hillert J,[2] Kockum I,[2,4] Stridh P,[2,4] Montgomery S,[1,5,6]

[1]Clinical Epidemiology Division, Karolinska Institutet (KI) Sweden; [2]Centre for Molecular Medicine, Karolinska University Hospital, Sweden; [3] Centre of Occupational and Environmental Medicine, Region Stockholm, Sweden; [4] Dept. of Clinical Neuroscience, KI Sweden; [5] Clinical Epidemiology and Biostatistics, Örebro University Sweden; [6] Dept. of Epidemiology and Public Health, University College London UK.

INTRODUCTION

Spasticity is a common complication of MS and influences function and quality of life.[1] Its prevalence is estimated between 50-80% with various levels of severity among MS patients.[2]

Knowledge of specific risk factors for spasticity is incomplete as the few studies of spasticity are cross-sectional and include only prevalent MS patients.[3]

To our knowledge, no study has explored specific risk factors for spasticity, including genetic risk factors among incident MS patients.

AIM

To characterize potential risk factors for spasticity indicated by treatment using a cohort study among Swedish prevalent and incident MS patients.

METHODS

People participating in Swedish MS studies, initially genotyped with the MS Replication Chip were included. Data were linked to national registers, and individuals with incident or prevalent MS (N=1826 iMS, N= 3519 pMS) were identified using ICD codes, and the MS Register.

The outcome was the first pharmaceutical spasticity treatment, identified using ATC codes for approved spasticity treatment in Sweden.

Genome-wide association analysis (GWA) of ever vs never spasticity included all MS patients genotyped at deCODE Genetics using Human Omni Express, a GWA genotype chip (N=5065).

People with spasticity prior to MS diagnosis or start of follow-up were (1Jul2006) were excluded in Cox regression models estimating hazard ratios (HR), following patients until spasticity, death or 31Dec2014. Age was the underlying timescale.

RESULTS

Table 1: Demographic characteristics.

	Incident		Prevalent	
Characteristic at study entry	*No Spasticity*	*Spasticity*	*No Spasticity*	*Spasticity*
N	**1376**	**450**	**2347**	**1172**
Sex				
Male	376(27.33)	133(29.56)	578(24.63)	324(27.65)
Female	1000(72.67)	317(70.44)	1769(75.37)	848(72.35)
Mean age, years (SD, min-max)	39.01(0.29, 18.26-65.13)	42.52(0.49, 18.02-64.79)	47.67(0.24, 19.37-83.96)	49.29(0.32, 20.71-80.79)
Education				
Primary education	98(7.12)	55(12.22)	269(11.46)	193(16.47)
Secondary education	637(46.29)	227(50.44)	1087(46.31)	534(45.56)
Tertiary education	641(46.58)	168(37.33)	991(42.22)	445(37.97)
Comorbid diseases				
Depression	220(15.99)	114(25.33)	496(21.13)	384(32.76)
Mean age at MS diagnosis, years(SD, min-max)	38.93(0.29, 18.06-64.82)	42.44(0.49, 18.02-64.71)	38.93(0.22, 18.04-64.88)	40.47(0.31, 18.09-64.86)
Mean age at MS onset, years(SD, min-max)	34.74(0.29, 8.75-63.59)	38.01(0.51, 10.37-62.67)	32.54(0.21, 6.13-62.92)	33.65(0.31, 11.75-62.46)
Disease course				
Relapsing remitting MS	1154(83.87)	312(69.33)	1545(65.83)	577(49.23)
Primary progressive MS	52(3.78)	58(12.89)	138(5.88)	133(11.35)
Secondary progressive MS	67(4.87)	54(12.00)	589(25.10)	432(36.86)
Unknown MS disease course	103(7.49)	26(5.78)	75(3.20)	30(2.56)
DMT use	**1237**	**336**	**2011**	**917**
No DMT use	58(4.68)	29(8.63)	355(17.65)	158(17.23)
Moderately effective DMT	1032(83.29)	267(79.46)	1595(79.31)	739(80.59)
Highly effective DMT	149(12.03)	40(11.90)	61(3.03)	20(2.18)

Table 2: The association of incident MS characteristics as risk factors for spasticity. All variables except sex and age at onset are time-varying. Models adjusted for age, county of residence and education.

	Model 1		Model 2		Model 3		Model 4	
	HR	CI	HR	CI	HR	CI	HR	CI
Disease course								
RRMS	1.00	1.00,1.00	1.00	1.00,1.00	1.00	1.00,1.00		
PPMS	2.46	1.77,3.42	1.79	1.02,3.14	2.32	1.65,3.27		
SPMS	2.41	1.77,3.28	2.47	1.55,3.95	2.36	1.73,3.22		
Unknown	0.82	0.48,1.40	0.58	0.21,1.62	0.82	0.48,1.40		
Sex								
Male	1.00	1.00,1.00	1.00	1.00,1.00	1.00	1.00,1.00	1.00	1.00,1.00
Female	0.96	0.77,1.20	1.13	0.80,1.60	0.97	0.78,1.20	1.08	0.77,1.52
Years with MS								
<0.5	1.00	1.00,1.00	1.00	1.00,1.00	1.00	1.00,1.00	1.00	1.00,1.00
>=0.5 to <1	0.36	0.25,0.52	0.32	0.18,0.58	0.37	0.26,0.54	0.32	0.18,0.58
>=1 to <2	0.33	0.24,0.45	0.38	0.24,0.59	0.34	0.25,0.46	0.38	0.24,0.61
>=2 to <3	0.26	0.18,0.36	0.31	0.19,0.52	0.27	0.19,0.38	0.31	0.19,0.52
>=3 to <6	0.23	0.17,0.30	0.26	0.17,0.41	0.24	0.17,0.32	0.26	0.16,0.40
>=6	0.15	0.10,0.23	0.18	0.09,0.35	0.16	0.10,0.25	0.18	0.09,0.35
Age at MS onset	1.02	1.00,1.04	1.05	1.02,1.08	1.02	1.01,1.04	1.04	1.02,1.07
Vascular disease	2.33	1.47,3.69	1.64	0.68,3.94	2.39	1.51,3.79	1.04	0.44,2.47
Depression	1.85	1.51,2.27	2.09	1.53,2.84	1.86	1.52,2.29	2.22	1.63,3.02
EDSS								
0			1.00	1.00,1.00			1.00	1.00,1.00
1-1.5			1.68	0.90,3.12			1.65	0.89,3.08
2-2.5			3.23	1.79,5.82			3.28	1.81,5.91
3-3.5			3.35	1.78,6.33			3.38	1.78,6.41
4+			4.71	2.33,9.53			5.52	2.72,11.22
First DMT								
No DMT					1.00	1.00,1.00	1.00	1.00,1.00
Moderately effective DMT					0.86	0.67,1.10	0.84	0.58,1.21
Highly effective DMT					1.13	0.75,1.72	0.94	0.55,1.61

Table 3: Potential risk factors for spasticity among incident and prevalent MS patients.

	Model 1		Model 2		Model 3	
Incident MS	HR	CI	HR	CI	HR	CI
Concussion or TBI*	/	/	/	/	/	/
Coronary artery disease	2.05	0.63,6.75	2.42	0.86,6.80	3.11	1.17,8.23
Vascular disease	1.99	1.22,3.23	1.92	1.19,3.09	2.14	1.36,3.39
Diabetes						
Type I	2.62	1.07,6.43	2.42	1.02,5.74	2.51	1.19,5.28
Type II	0.43	0.10,1.97	0.39	0.08,1.97	0.41	0.08,2.01
Type unknown	2.07	0.16,27.57	2.68	0.26,27.93	3.06	0.31,30.16
Stroke	0.72	0.32,1.64	0.78	0.37,1.65	0.79	0.38,1.64
Depression	1.70	1.39,2.08	1.61	1.32,1.97	1.86	1.53,2.26
Parkinson's disease	3.20	1.38,7.43	3.61	1.73,7.54	3.55	1.68,7.50
Prevalent MS						
Concussion or TBI	1.69	0.77,3.69	1.44	0.64,3.23	1.44	0.65,3.22
Coronary artery disease	1.15	0.76,1.74	1.17	0.78,1.76	1.19	0.79,1.78
Vascular disease	1.25	0.99,1.58	1.23	0.97,1.55	1.24	0.98,1.56
Diabetes						
Type I	1.24	0.58,2.67	1.38	0.71,2.69	1.39	0.72,2.67
Type II	0.85	0.50,1.46	0.83	0.48,1.45	0.83	0.48,1.45
Type unknown	1.08	0.22,5.24	0.95	0.18,4.85	0.96	0.19,4.91
Stroke	1.24	0.88,1.74	1.29	0.92,1.82	1.29	0.92,1.81
Depression	1.70	1.39,2.08	1.61	1.32,1.97	1.86	1.53,2.26
Parkinson's disease	1.54	0.98,2.42	1.47	0.95,2.30	1.48	0.95,2.30

Individuals with incident and prevalent MS. Attained age as the underlying timescale. Risk factors for spasticity as timevarying covariates. All models included each specific risk factor separately. Model 1 adjusted for age, county of residence at MS diagnosis, and highest attained education Model 2 adjusted for disease course as a timevarying covariate. Model 3 adjusted for years with MS as an additional timescale. Robust standard errors used to calculate confidence intervals for all models including timevarying covariates.
* Concussion or TBI estimates could not be computed as few individuals experienced concussion or TBI.

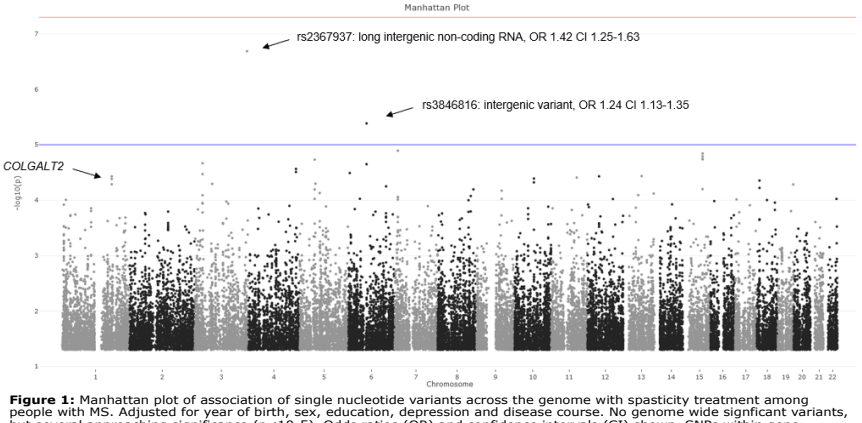

Figure 1: Manhattan plot of association of single nucleotide variants across the genome with spasticity treatment among people with MS. Adjusted for year of birth, sex, education, depression and disease course. No genome wide signficant variants, but several approaching significance (p<10-5). Odds ratios (OR) and confidence intervals (CI) shown. SNPs within gene *COLGALT2* reduced in significance after adjustment.

CONCLUSIONS

- Most spasticity treatment was initiated within the first 6 months of MS diagnosis among incident MS patients, and among prevalent MS patients from 0.5-3 years of diagnosis.
- Disease course and EDSS have highest magnitude association to spasticity treatment, however other markers of disease severity such as relapses, and increasing comorbid disease burden also associated among both incident and prevalent MS patients.
- Diagnoses or treatment of Parkinson's disease among incident MS patients was strongly asssociated with treatment for spasticity. Other comorbid diseases such as depression, and type I diabetes are more strongly associated among incident MS patients.
- Preliminary genetic analyses indication that several loci may be associated to spasticity. These will be investigated further, and should be reconfirmed.

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Kelsi Smith iBSc, MMSc | PhD Candidate
Trained in molecular biology, neuroscience and epidemiology.
Passionate about research in multiple sclerosis and neurological diseases.
Contact me: kelsi.smith@ki.se

Karolinska Institutet