J Neurol (2013) 260:1258–1262
DOI 10.1007/s00415-012-6785-y

ORIGINAL COMMUNICATION

Historical changes of seasonal differences in the frequency of multiple sclerosis clinical attacks: a multicenter study

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Received: 22 September 2012 / Revised: 30 November 2012 / Accepted: 1 December 2012 / Published online: 21 December 2012

Abstract Previous papers show discordant patterns of monthly and seasonal differences in the frequency of multiple sclerosis relapses. Attacks are more often reported in spring and summer, but there are many variations, mainly as to summer peaks. This paper, an MSBase collaboration substudy, reports multiple series of relapses from 1980 to 2010, comparing ultradecennal trends of seasonal frequency of attacks in different countries. The MSBase international database was searched for relapses in series recording patient histories from 1980 up to 2010. The number of relapses by month was stratified by decade (1981–1990, 1991–2000, 2001–2010). Positive spring versus summer peaks were compared by odds ratios; different series were compared by weighted odds ratio (Peto OR). Decade comparison of the 1990s versus 2000s shows inversion of spring–summer peak (2000s = March; 1990s = July), significant in the whole group (Peto odds ratio = 1.31, CI = 1.10–1.56, $p = 0.003$) and in Salerno series (OR = 1.97, CI = 1.14–1.40). The global significance persisted also excluding Salerno series (Peto odds ratio = 1.25, CI = 1.04–1.50, $p = 0.002$). Multicentric data confirm a summer peak of relapses in the 1991–2000 decade, significantly different from the spring peak of 2001–2010. Seasonal frequency of relapses shows long-term variations, so that other factors such as viral epidemics might have more relevance than ultraviolet exposure.

Keywords Multiple sclerosis · Relapse · Seasonal variation · Temporal trends

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Background

Previous papers show, in patients with multiple sclerosis (MS), discordant patterns of monthly and seasonal differences in the frequency of relapses. Peaks of attacks are more often reported in spring, also supported by a meta-analysis [1–3], and in summer, up to 2010 [4–6], but there are many variations, mainly as to summer peaks. Other papers show higher frequency in winter [7], or multiple peaks (summer and winter [8], summer and spring [9]), a negative peak in late summer [10], and also only small [11] or no monthly differences [12, 13].

Latitude and climate can account only partly for the differences: summer peaks seem to be reported mainly in warmer countries [3, 6, 9], and more spring or winter attacks in northern countries [1, 3, 7], but there are warm

countries with no peaks in summer [10, 11], or summer peaks (such as in North Dakota) [5]. In the Southern Hemisphere the main peak is not in summer but in autumn [13]. Papers report a positive correlation with temperature [2, 8, 13], and a negative correlation with precipitation [14]; others do not find any correlation [12].

The viral hypothesis is the most investigated factor possibly explaining seasonal differences; however, vitamin D, which is supposed to be one of the factors for latitude differences [15–23], is also taken into consideration for the spring peaks of relapses.

In a polycentric study, global data from the MSBase registry [24, 25], showed different findings: a significant seasonal variation in both hemispheres, with a main peak in June, on about 22,000 relapses, confirmed on about 5,000 first events [24], and different spring peaks (April in northern, October in southern countries) with secondary peaks in autumn, on 14,000 relapses [25].

A retrospective observational study using high-frequency serial magnetic resonance imaging (MRI), performed in 1991–1993 on 44 cases [26], shows that the peak of T2 MRI activity was in summer (March–August), strongly correlated with higher temperatures.

Recent data published by one of us [27], stratifying in the long term the seasonal frequency, found significant differences between the last two decades, with a spring peak in the 2000s versus a summer peak in the 1990s. A MSBase collaboration substudy, including only series which recorded relapses in different decades, was proposed to confirm these data.

This paper reports the data of this MSBase collaboration substudy, based on multiple series of relapses reported from 1980 to 2010, so as to compare ultradecennal trends of seasonal frequency of attacks in different countries.

Methods

MSBase is an ongoing, longitudinal, strictly observational registry open to all practicing neurologists worldwide. In collaboration with participating physicians, the MSBase registry establishes a unique international database dedicated to sharing, tracking, and evaluating outcomes data in MS [28].

Currently, seven series from six countries are included in the substudy: Argentina (Buenos Aires), Belgium (Brussels), Canada (Montreal), Italy (Chieti), Italy (Salerno), Spain (Madrid), and Turkey (Trabzon).

To minimize selection bias, only patients with complete data were included. Demographic data are presented in Table 1.

Only attacks with a definite onset were considered; dates conventionally used to indicate relapses of unknown onset were excluded: January 1 for all series, June 1 for Spain, June 15 for Italy, Chieti.

Criteria for diagnosis of relapses were: new symptoms or signs lasting at least 24 h; exclusion of pseudorelapses or paroxystic episodes; minimal interval between two attacks of at least 30 days [29].

Austral hemisphere series (Argentina) was registered, seasonally, from July (first month) to June (last).

The number of relapses by month was calculated and stratified by decade (1981–1990, 1991–2000, 2001–2010). Positive spring (March) versus summer (July) peaks were compared by odds ratios and chi-square tests; different series were not cumulated, but compared by weighted odds ratio (Peto).

Results

The total number of relapses by month is summarized in Table 2. The 1970s and 1980s decades show of course a lower number of relapses, because MSBase registries started in the late 1990s, and previous data are anamnestic. So, only the last two decades were compared.

Relapse numbers for 1990 (1991–2000) and 2000 (2001–2010) decades are tabulated in Tables 3 and 4; The same data are shown graphically in Fig. 1. The number of relapses in 1990 has its peak (mode) in July (Fig. 1a); in 2000 the peak is in March (Fig. 1b).

However, the single series show many variations and cannot be simply cumulated, so we calculated and compared spring versus summer peaks, series by series and decade by decade. Statistical comparison between the two last decades is shown in Figs. 2 and 3. Decade comparison of the 1990s versus the 2000s shows inversion of spring–summer peak (March in 2000s, July or August in 1990s), which is significant in the whole group (Peto odds ratio = 1.31, CI = 1.10–1.56, $p = 0.003$) and in Salerno series (OR 1.97, CI 1.14–1.40) (Fig. 2).

The cumulative significance was confirmed (Peto odds ratio = 1.25, CI = 1.04–1.50, $p = 0.002$) also in a sensitivity analysis excluding Salerno series, which is the only one showing significant results even alone (Fig. 3).

Discussion

There are no previous multicentric studies comparing different decades; the only paper, to our knowledge, addressing this issue is a single-center study by Iuliano [27].

In the present study we widened the population and geographical areas under study.

Table 1 Demographic data by series: number of patients, age at onset range (mean; standard deviation), disease duration mean (range), total relapse number

Series	Patients	Age at onset, range (mean; SD), years	Disease duration, mean (range), years	Relapses
Argentina	197	12–68 (29.83; 13.64)	8.78 (1–49)	561
Belgium	285	7–69 (32.33; 15.04)	8.56 (0–22)	1,233
Canada	925	5–72 (30.82; 33.32)	11.34 (0–35)	4,639
Italy-C	1,111	6–75 (33.55, 33.64)	8.97 (0–52)	3,854
Italy-S	262	11–72 (32.75; 18.67)	6.94 (0–29)	1,179
Spain	642	5–71 (32.30; 10.74)	9.88 (1–42)	1,979
Turkey	519	10–74 (34.07; 24.02)	4.27 (1–28)	1,526

Table 2 Total relapses: distribution by month

Series	January	February	March	April	May	June	July	August	September	October	November	December
Argentina[a]	31	31	33	26	38	30	14	38	41	34	34	39
Belgium	46	83	104	93	94	86	81	93	82	88	85	108
Canada	157	319	334	387	330	311	377	278	313	358	294	345
Italy-C	223	282	328	295	335	266	340	242	274	204	266	275
Italy-S	67	74	141	93	100	92	111	96	83	94	86	88
Spain	60	149	197	177	185	50	173	155	160	166	139	154
Turkey	59	116	114	134	152	121	105	106	86	90	94	98

[a] Argentina: January = July; December = June

Table 3 Relapse number 1991–2000: distribution by month

Series	January	February	March	April	May	June	July	August	September	October	November	December
Argentina[a]	14	15	10	11	13	15	7	17	21	15	12	21
Belgium	15	25	40	31	31	31	33	38	31	28	26	47
Canada	40	110	120	131	131	110	148	103	116	123	110	137
Italy-C	73	87	105	111	113	86	124	96	96	10	104	94
Italy-S	27	17	36	42	35	33	44	35	32	37	36	30
Spain	6	45	40	41	45	4	43	36	47	43	32	37
Turkey	14	27	18	16	22	20	21	20	23	18	16	14
Total	189	326	369	383	390	299	420	345	366	274	336	380

[a] Argentina: January = July; December = June

Table 4 Relapse number 2001-2010: distribution by month (* Argentina: Jan = Jul; Dec = Jun)

Series	January	February	March	April	May	June	July	August	September	October	November	December
Argentina[a]	16	15	22	14	23	13	7	20	20	18	16	18
Belgium	30	52	53	56	62	52	47	48	46	56	56	55
Canada	95	166	175	198	156	151	163	139	147	178	144	150
Italy-C	138	180	209	169	196	162	204	133	160	180	153	165
Italy-S	35	50	95	50	58	47	59	59	47	49	45	55
Spain	53	99	154	135	137	46	128	115	112	119	105	116
Turkey	42	88	90	116	126	100	81	84	61	68	75	83
Total	409	650	798	738	758	571	689	598	593	668	594	642

[a] Argentina: January = July; December = June

Our multiple series confirm the high variability shown in the literature (see "Background") and can reasonably explain this variability.

Previous papers [1–14] do not seem to show definitive trends for spring or summer peaks, also when classified for year of publication, except, possibly, for some papers published after 2004 and showing multiple and hardly statistically assessable peaks, mainly in spring and summer [8, 10, 11].

There are, however, papers confirming a spring peak published in the 2000s [2, 25], and a summer peak published in the 1990s [4, 5]; in addition, a recently published paper based on MRI serial data collected in 1991–1993 also shows a significant summer peak of MRI activity [26].

There are limitations: as the number of patients and of recorded attacks is, in all series, increasing with time, reliable comparison among different decades was possible only for the last two. It is hardly possible that further addition of patients could allow more comparisons, because recalling old events is increasingly difficult with time.

Another limitation is the impossibility of obtaining old data about climate, epidemics, and environmental variables to study possible correlations, which is even more difficult as they would need to be aggregated as mean decade data.

Anyway, variables such as epidemics or local environment factors may be changing over time; other environmental factors, such as UV exposure or climate, are certainly more stable along the course of a year.

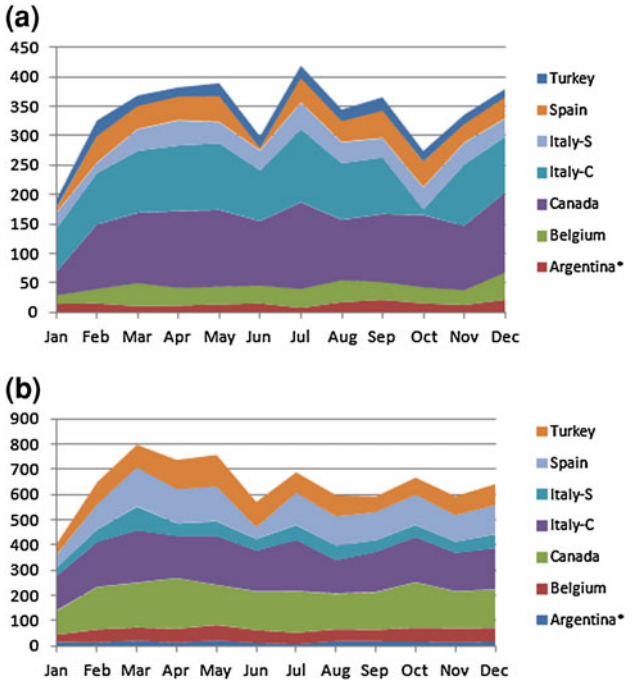

Fig. 1 Number of relapse by series (*Y*-axis), distribution by month (*X*-axis): **a** 1991–2000, **b** 2000–2010

Conclusions

Comparison of series from multiple geographical areas confirms a spring peak of relapses in the 2000–2009 decade, contrary to the 1990–1999 one, where a summer peak is evident. Independently from the year period of peaks,

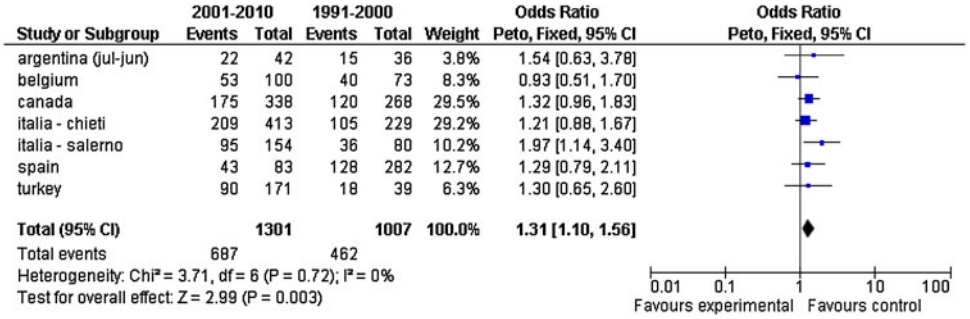

Fig. 2 Comparison of spring peak of relapses (events) versus summer peak (Total = spring and summer peak), series by series, by Peto odds ratio

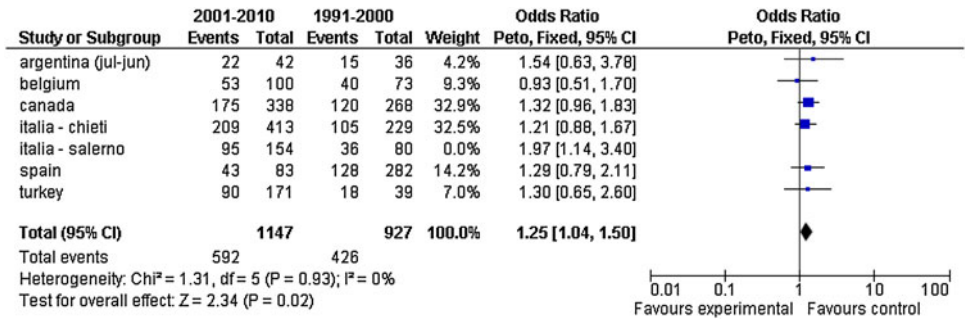

Fig. 3 Comparison of spring peak of relapses (events) versus summer peak (Total = spring and summer peak), series by series, by Peto odds ratio: sensitivity analysis (Salerno series excluded from calculations)

seasonal frequency of relapses might vary in the long term, due to other factors such as viral epidemics or other environmental variables, whose effect could be more evident than climate, ultraviolet exposure, and correlated factors.

Conflicts of interest Gerardo Iuliano has had travel/accommodation/meeting expenses funded by Bayer Schering, Sanofi Aventis, Merck Serono, Novartis, and Biogen Idec, Cavit Boz, Edgardo Cristiano, and Pierre Duquette declare no conflicts of interest. Alessandra Lugaresi has received honoraria or grants from Bayer Schering, Biogen Idec, Merck Serono, Sanofi Aventis, Novartis, and Teva. Dr. Oreja-Guevara has participated in clinical trials and other research projects promoted by Biogen Idec, GSK, Merck-Serono, Teva, and Novartis. Vincent Van Pesch has received compensation for serving on an advisory board for Biogen Idec (2010–11), travel/accommodations/meeting expenses funded by Bayer Schering, Sanofi Aventis, Merck Serono, Novartis, and Biogen Idec, and honoraria for speaking engagement funded by Biogen Idec (2011).

Ethical standard All human studies must state that they have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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