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## Multiple sclerosis prevalence among Sardinians: further evidence against the latitude gradient theory

**Abstract** A descriptive epidemiological survey was extended to the whole province of Sassari, northern Sardinia between latitudes 40°30' N and 41° N. Results showed a crude total prevalence rate of 144.4 per 100 000 on prevalence day (31 December 1997), and an onset-adjusted prevalence rate of 149.7 per 100 000. The total average annual incidence rate was 4.9 per 100 000 for the whole time interval studied (1968-1997), having increased from 2.0 in 1968-1972 to 6.8 in the last quinquennium considered. A substantial improvement in MS case ascertainment due to the introduction of new diagnostic procedures might account for such rates in Sardinia as well as in other Italian regions. However, when comparing our data with those obtained in the province of Ferrara, in the same time frames (1968-1997), a nine-fold versus a five-fold increase of MS prevalence was detected in Ferrara and Sassari, respectively. MS incidence temporal trend also notably increased in Sassari, but remained substantially stable in Ferrara. The progressive shortening of the time interval between clinical onset and diagnosis, and the proportion of benign-mild MS cases, were similar in both studies, thus suggesting a similar diagnostic accuracy. In our opinion, the repeatedly assessed increase of MS frequency in our province, at least partially does represent an actual rise of MS risk

among Sardinians, thus disproving the latitude gradient-based theory (i.e. prevalence rates correlate with geographical latitudes) and supporting the hypothesis of a "Sardinian focus" of MS in a genetically susceptible population.

**Key words** Multiple sclerosis • Prevalence • Incidence • Sardinia

### Introduction

Small population-based studies conducted by our research group in northern Sardinia, insular Italy, since 1980 [1] indicated that prevalence rates of multiple sclerosis (MS) have increased more than two or three times that which has been observed in the rest of continental and insular Italy in the same time interval. The aim of the present study was to extend our investigation of MS frequency to the entire population of the Sardinian province of Sassari, which constitutes one-third of the population of the island, in order to update and confirm what appears to be a temporal trend.

### Methods

The study covered the province of Sassari, in northern Sardinia, that lies between latitudes 40°30' N and 41° N. It has an area of 7520 square kilometers and encompasses 89 municipalities. In the 1991 census, the total population was 454 904 (224 984 men and 229 920 women). Over the past 30 years, the population of the province increased from 381 191 to 454 904. The population denominators were calculated using log incremental rates for intercensus data. Migration flow was moderate: in 1995, 1.7% of the total population was registered as resident from other Italian provinces and from foreign countries, whereas 1.6% had moved away from the study area. The population consisted almost entirely of Sardinian natives, the proportion of residents born outside the province of Sassari being negligible. As a result we believe that generalizations to the popula-

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tion of the whole island are warranted. The Sardinian population is ethnically and culturally homogeneous and distinct, as indicated by genetic, linguistic and historical studies. In particular, the genetic distances between Sardinia and the rest of Italy and Europe are 10-fold higher than between non-Sardinian Italians and Europeans, although Sardinians share the same Caucasoid origin [2].

#### Case collection and ascertainment

In 1995, a register of MS cases was created at the Neurological Clinic of the University of Sassari, to include patients diagnosed as suffering from MS according to the Poser criteria [3] for clinical or laboratory supported definite MS (CDMS, LSDMS), and clinical or laboratory supported probable MS (CPMS, LSPMS). Other autoimmune and/or immunomediated and infectious diseases such as primary and secondary CNS vasculitis, post-infectious leukoencephalopathy and other demyelinating disorders were ruled out by means of laboratory tests and neuroimaging, in addition to history and neurological examination.

#### Results

On prevalence day (31 December 1997), 686 subjects living in the province of Sassari had been diagnosed as suffering from MS (492 women and 194 men). Using as denominator the 1997 population, the crude overall prevalence rate was 144.4 per 100 000 (standardized rate of 141). The highest rates were observed in the age range 30-49 years, ranging from 300 to 326 in different age groups. For women, in particular, the highest rates were assessed in the age group 30-34 years (457 per 100 000).

Considering the patients who, on prevalence day, were already symptomatic but not diagnosed yet, onset-adjusted total prevalence rate was of 149.7 per 100 000. The mean age on prevalence day was  $42.4 \pm 12.2$  years:  $41.8 \pm 12.1$  for women, and  $43.6 \pm 11.9$  for men.

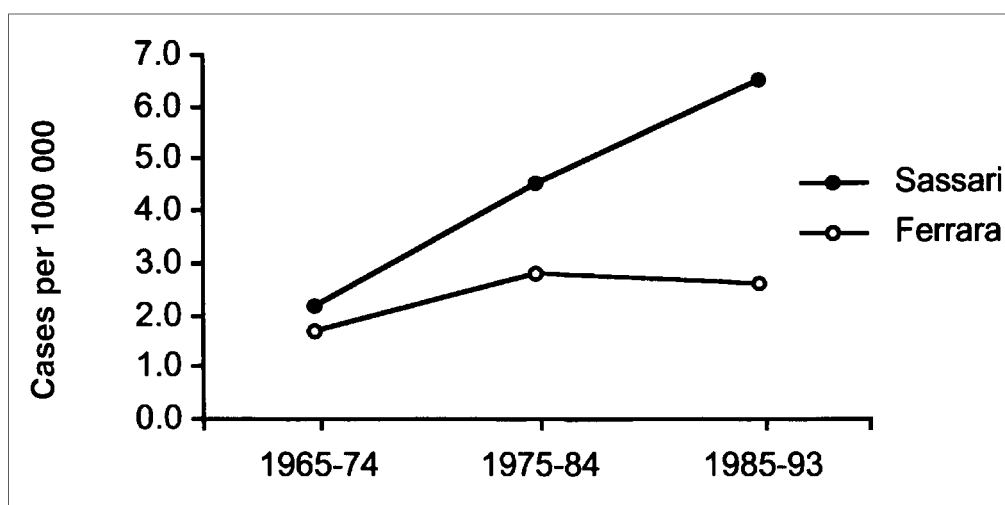
Incidence was studied for the period 1 January, 1968 to 31

December, 1997. During that period of 30 years, 637 patients (455 women and 182 men) had the onset of MS while living in the study area. The mean age at onset was  $28.0 \pm 9.0$  years ( $27.5 \pm 8.9$  for women and  $29.5 \pm 8.8$  for men). The average annual incidence for the entire period was 4.9 per 100 000, 6.9 for women and 2.8 for men. The highest rates were noted in the age groups between 20 and 34 years for both sexes. The total incidence rates increased over time from values of 2.0 per 100 000 in the period 1968-1972 to 6.8 in the interval 1993-1997 (from 2.4 to 9.2 for women and from 1.6 to 4.2 for men).

#### Conclusions

Previous investigations demonstrated that Sardinia is a high-risk area for MS. The present research, a "spider" kind of population-based survey [4], is an update of MS prevalence to 31 December 1997 and a study of the temporal trend of MS incidence between 1968 and 1997 in the province of Sassari. Observed MS prevalence rates are notably higher than those expected in relation to Sardinia's latitude. We ruled out an increased disease duration due to longer survival, an increased number of benign or mild cases due to greater diagnostic accuracy and awareness for the disease, improved epidemiological procedures, influx of people in the high-risk age groups, and immigration of individuals from a population genetically at higher risk for MS. A comparison with a survey in the province of Ferrara, in northern Italy in 1993 [5], reveals that prevalence rates in the province of Sassari are nearly three-fold greater and that better diagnostic accuracy and improved epidemiological methodology cannot therefore fully account for the observed increased prevalence.

A significant increase of new MS cases per year was observed in the 3 decades considered. Comparing the trend of the time lag between clinical onset and diagnosis in our study versus Ferrara [5], no difference was detected to be possibly responsible for the increased prevalence. Instead, a clear dif-



**Fig. 1** Temporal trends of MS incidence rates in the provinces of Sassari and Ferrara, in the period 1965-1993

ference in the incidence trend over time was observed (Fig. 1).

Our results are consistent with those previously observed in Sardinia by the same group of researchers, confirming that Sardinia is among the areas at highest frequency of MS in the world [4]. Better diagnostic accuracy does not fully account for the steady increase of MS frequency observed over a long period of time by means of repeated assessments. A true rise of MS risk in Sardinia secondary to biological factors is therefore hypothesized. Such high rates appear to be in contrast with the latitude gradient-based theory according to which MS prevalence rates correlate with geographical latitudes, and support the hypothesis of a "Sardinian focus" of MS in a genetically susceptible population.

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**Sommario** *Il presente lavoro è un'indagine epidemiologica descrittiva estesa all'intera provincia di Sassari, Sardegna settentrionale, latitudine 40°30' N e 41° N. I risultati mostrano un tasso crudo di prevalenza totale di 144.4 per 100 000 al giorno di prevalenza 31 dicembre 1997, ed un tasso di prevalenza totale aggiustato per l'esordio di 149.7 per 100 000. Il tasso di incidenza totale medio era di 4.9 per 100 000/anno per l'intero intervallo di tempo studiato (1968-1997), incrementato da 2.0 nel periodo 1968-1972 a 6.8 nel periodo 1993-1997. Un sostanziale miglioramento nell'accertamento dei casi di SM legato all'introduzione di nuove procedure diagnostiche potrebbe giustificare tali tassi in Sardegna, ma tale fenomeno si è verificato anche per altre regioni italiane. Tuttavia, nel confrontare i nostri dati con quelli ottenuti nella provincia di Ferrara nello stesso inter-*

*vallo di tempo (1968-1997), l'incremento della prevalenza di SM nella terza decade studiata è stato nove volte superiore rispetto alla prima a Sassari e cinque volte superiore a Ferrara. Veniva anche osservato un notevole aumento dell'incidenza a Sassari, che tuttavia restava sostanzialmente stabile a Ferrara. Il progressivo accorciamento dell'intervallo di tempo tra l'esordio clinico di malattia e la diagnosi e la proporzione di casi benigni-lievi di SM erano simili in entrambi gli studi a dimostrazione di una simile accuratezza diagnostica. A nostro avviso, l'incremento della frequenza di SM nella nostra provincia ripetutamente accertato, rappresenta, almeno parzialmente, un effettivo aumento del rischio di SM tra i Sardi, in contrasto con la teoria del gradiente latitudinale ma sostenendo l'ipotesi di un "focus sardo" di SM in una popolazione geneticamente suscettibile.*

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