Multiple Sclerosis: Studies of the Interferon system and search for infectious agents

Bergkvist, My

2005

ELSEVIER

Journal of Neuroimmunology 65 (1996) 163–165

Journal of Neuroimmunology

Short Communication

No genetic linkage between multiple sclerosis and the interferon α/β locus

My Bergkvist [a,*], Tommy Martinsson [b], Pierre Åman [c], Magnhild Sandberg-Wollheim [a]

[a] *Department of Neurology, University Hospital, S-22185 Lund, Sweden*
[b] *Department of Clinical Genetics, East Hospital, S-41685 Gothenburg, Sweden*
[c] *Department of Clinical Genetics, University Hospital, S-22185 Lund, Sweden*

Received 12 July 1995; revised 22 December 1995; accepted 25 January 1996

Abstract

Multiple sclerosis (MS) is probably caused by an interaction of genetic and environmental factors. The genetic component is reflected by a ten-fold higher concordance rate in monozygotic (27%) compared to dizygotic (3%) twin pairs. Treatment with interferon was recently reported to have a favorable effect in patients with relapsing-remitting MS. In the present familial study, we have investigated the possibility of a genetic association between the highly polymorphic Interferon $\alpha\beta$ locus and the development of MS. Based on our data, we conclude that there is no linkage between the Interferon $\alpha\beta$ locus and MS.

Keywords: Multiple sclerosis; Interferon; Genetic linkage; DNA

1. Introduction

MS is a neurodegenerative disease with an incidence of 3–5 per 100 000 in the nordic countries. The etiology is not known but the results from many studies of MS suggest that the disease is caused by an interaction of genetic and environmental factors (Ebers and Sadovnick, 1994).

The genetic component is reflected by the higher concordance rate in monozygotic (27%) compared to dizygotic (3%) twin pairs (Sadovnick et al., 1993; Mumford et al., 1994) and a higher prevalence of the disease in first degree relatives of patients (Sadovnick and Baird, 1988).

Results from family studies suggest that susceptibility-associated genes are located within the HLA complex on the short arm of chromosome 6. The myelin basic protein (MBP) gene and the tumor necrosis factor genes (TNF) are other candidate genes for MS susceptibility, although results from family studies of the former are contradictory (Tienari et al., 1992; Graham et al., 1993; Rose et al., 1993).

CSF T-cell clones from patients with MS have been found to produce more interferon gamma (IFNγ) and TNFα than control cell clones from healthy donors (Benvenuto et al., 1992). There are also results indicating that TNFα levels correlate with disease progression and severity (Sharief and Thompson, 1992).

Treatment with interferon β (IFNβ) was recently reported to have a favorable effect in MS patients with relapsing-remitting disease. A significant reduction in exacerbation rates, severity of exacerbations, and accumulation of MRI abnormalities was noted (The IFNβ Multiple Sclerosis Study Group, 1993; Paty et al., 1993). The mechanism of action of IFNβ that is responsible for these positive results is still unknown. Results from earlier studies show that IFNβ has the ability to inhibit or decrease IFNγ (Panitch et al., 1987; Noronha et al., 1991, 1993) and to augment defective suppressor cell function in MS patients (Noronha et al., 1990).

IFNγ enhances antigen presentation by increasing class II MHC antigens and thus IFNβ counteracts these effects (Panitch et al., 1989). This may indicate that the IFN system is somehow involved in the development of MS.

The IFNα and IFNβ genes share extensive homology and are located closely linked to each other in the same or adjacent bands on the short arm of chromosome 9. The IFNγ gene is located on the long arm of chromosome 12 and shows no homology with IFNα or β (Ohlsson et al.,

* Corresponding author. Tel. +46 (46) 171 421; Fax +46 (46) 158 919.

PII S0165-5728(96)00018-5

1985). A high degree of polymorphism has been identified in the human IFNα and β gene regions (Ohlsson et al., 1985).

In the present familial study we investigated the possibility of a genetic association between the IFN$\alpha\beta$ locus and the development of MS.

2. Material and methods

2.1. Patients and controls

126 Swedish individuals belonging to 24 unrelated families with at least two members with clinically definite MS by standard criteria (Poser et al., 1983) were studied. The patients consisted of 18 men and 33 women. The mean age of the patients was 48.3 years (range 28–71). The mean age at onset of the disease was 28.4 years (range 16–71). The onset age for four of the patients was not known. Clinical subtypes were not defined. Unaffected members of the families had an average age of 60.3 years (range 27–87); 41 were men and 34 were women. The controls were healthy blood donors, 63 men and 78 women, of the same ethnic origin as the patients. None of the controls were related to the patient families.

2.2. Method

DNA was isolated from peripheral blood and a microsatellite polymorphism in the IFNα locus was analyzed by PCR with primers TGCGCGTTAAGTTAATTGGTT and GTAAGGTGGAAACCCCCACT (19). The samples were predenatured at 98°C for 2 min followed by 30 cycles of 94°C for 30 s, 53°C for 30 s, and 72°C for 40 s.

2.3. Statistics

Two-point linkage analysis was performed with the MLINK program from the LINKAGE 5.1 package (Lathrop et al., 1984). The model applied for analyses was autosomal dominant inheritance, and several different levels of penetrance were tested. A gene frequency of the disease allele of 0.01 was used for the calculations. For affected sib-pair analysis, the ESPA program (version 2.2) by Sandkuyl (1989) was applied. Also partially informative sib-pairs were included in the analysis. The estimations for allele frequency used were those of the healthy control population presented in Table 1.

Table 1
IFNα/β allele frequencies in MS patients and controls

Allele	No. of chromosomes	
	MS patients [a]	Controls
1: 152 bp	1 (0.02)	5 (0.02)
2: 150 bp	11 (0.23)	54 (0.19)
3: 148 bp	23 (0.48)	147 (0.52)
4: 146 bp	5 (0.10)	34 (0.12)
5: 142 bp	8 (0.17)	42 (0.15)
6: 138 bp	0 (0.00)	0 (0.00)
Total	48	282

[a] One randomly chosen patient from each family.

Table 2
Two-point lod score values for linkage between MS in the 24 families and an IFNβ polymorphism

Penetrance	Recombination fraction (Θ)						
	0	0.01	0.05	0.1	0.2	0.3	0.4
0.2	−5.90	−4.96	−3.11	−1.95	−0.79	−0.26	−0.03
0.3	−6.33	−5.30	−3.36	−2.16	−0.91	−0.31	−0.04
0.5	−7.38	−6.05	−3.91	−2.59	−1.15	−0.42	−0.08

3. Results

We investigated 267 individuals, six of whom had a previously unknown allele comprising 152 base pairs. Five alleles with 138, 142, 146, 148, and 150 base pairs, respectively, have previously been reported in the polymorphic CA repeat of the IFNβ (Kwiatkowski and Diaz, 1992). Our MS patients and healthy controls showed a similar distribution of the alleles (Table 1). A homogeneity test of the two materials using one randomly chosen affected individual from each MS family gave a χ^2 of 1.28, $P = 0.86$.

Two-point linkage analysis using the MLINK program was performed on data from the 24 families. Several levels of penetrance for MS were tested. The results of these analyses are presented in Table 2.

At no Θ-value did the lod score (Z) exceed 0, i.e. no evidence of linkage was detected between MS and IFNβ in the family material. For instance, at penetrance level 0.3 linkage was excluded (i.e. Z below −2.0) until Θ reaches 0.11.

We also analyzed the family material with an affected sib-pair method using the ESPA program (Extended Sib-Pair Analysis; Sandkuyl, 1989). Data were available in 14 families with affected sib-pairs. The data for the ESPA analysis gave a χ^2 of 1.2 and $P = 0.84$. Therefore, evidence for an increased sharing of alleles, identical by descent (IBD) was not detected in the material.

4. Discussion

We have analyzed a group of Swedish MS families for possible genetic linkage between the disease and the IFNα/β locus. None of the 6 alleles were over-represented in the patient group and we conclude from the data analysis that there is no linkage between the IFNα/β and MS. These results indicate that the IFNα- and the tightly

linked IFNβ-locus are not involved in the development of the disease and also rule out the possibility of a defective IFNβ-production in MS patients. The positive effect of IFNβ treatment in MS is, therefore, not achieved by a reconstitution of IFNβ production.

Acknowledgements

This work was supported by grants from the Swedish Medical Research Council (Project No. B95-19X-06265-14B), the Medical Faculty of the University of Lund, the Thorsten and Elsa Segerfalk Foundation, and the Thelma Zoéga Foundation. M.B. was a recipient of a scholarship from Serono Nordic AB, Stockholm, Sweden.

References

Benvenuto, R., Paroli, M., Butinelli, C., Franco, A., Barnaba, V., Fieschi, C. and Balsano, F. (1992) Tumor necrosis factor-alpha and interferon-gamma synthesis by cerebrospinal fluid-derived T cell clones in multiple sclerosis. Ann. N.Y. Acad. Sci. 650, 341–346.

Ebers, G. and Sadovnick, A.D. (1994) The role of genetic factors in MS susceptibility. J. Neuroimmunol. 59, 1–17.

Graham, C.A., Kirk, C.W., Nevin, N.C., Droogan, A.G., Hawkins, S.A., McMillan, S.A. and McNeill, T.A. (1993) Lack of association between myelin basic protein gene microsatellite and multiple sclerosis. Lancet 341, 1596.

Kwiatkowski, D. and Diaz, M.O. (1992) Dinucleotide repeat polymorphism at the IFNA locus (9p22). Human Mol. Genet. 1, 658.

Lathrop, G.M., Laloucl, J.M. and Julier, C. (1984) Strategies for multilocus linkage analysis in humans. Proc. Natl. Acad. Sci. USA 81, 3443–3446.

Mumford, C.J., Wood, N.W., Kellar-Wood, H., Thorpe, T.W., Miller, D.H. and Compston, D.A.S. (1994) The British Isles survey of multiple sclerosis in twins. Neurology 44, 11–15.

Noronha, A., Toscas, A. and Jensen, M.A. (1991) IFN-beta down-regulates IFN-gamma production by activated T cells in Multiple Sclerosis. Neurology 41 (suppl. 1), 219.

Noronha, A., Toscas, A. and Jensen, M.A. (1993) Interferon beta decreases T cell activation and interferon gamma production in Multiple Sclerosis. J. Neuroimmunol. 46, 145–154.

Noronha, A., Toscas, A. and Jensen, M.A. (1990) Interferon beta augments supressor cell function in Multiple Sclerosis. Ann. Neurol. 27, 207.

Ohlsson, M., Feder, J., Cavalli-Sforza, L.L. and Von Gabain, A. (1985) Close linkage of alfa and beta interferones and infrequent duplication of beta interferon in humans. Proc. Natl. Acad. Sci. USA 82, 4473–4476.

Panitch, H.S., Folus, J.S. and Johnson, K.P. (1987) Recombinant Beta Interferon Inhibits Gamma Interferon Production in Multiple Sclerosis. Ann. Neurol. 22, 139.

Panitch, H.S., Folus, J.S. and Johnson, K.P. (1989) Beta interferon prevents HLA class II antigen induction by gamma interferon in MS (abstract). Neurology 39 (suppl. 1), 171.

Paty, D.W. and Li, D.K.B., The UBC MS/MRI Study Group and The IFNB Multiple Sclerosis Study Group. (1993) Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II.MRI analysis results of a multicenter, randomized double-blind, placebo-controlled trial. Neurology 43, 662–667.

Poser, C.M., Paty, D.W., Scheinberg, L., McDonald, W.I., Davis, F.A., Ebers, G.C., Johnson, K.P., Sibley, W.A., Silberberg, D.H. and Tourtelotte, W.W. (1983) New diagnostic criteria for multiple sclerosis:guidelines for research protocols. Ann. Neurology 13, 227–231.

Rose, J., Gerken, S., Lynch, S., Pisani, P., Varvil, T., Otterud, B. and Leppert, M. (1993) Genetic susceptibility in familial multiple sclerosis not linked to the myelin basic protein gene. Lancet 341, 1179–1181.

Sandkuyl, L.A. (1989) Analysis of affected sib-pairs using information from extended families. In: R.C. Elston, M.A. Spence, S.E. Hodge, et al. (Eds.), Multipoint Mapping and Linkage Based Upon Affected Pedigree Members: Genetic Analysis Workshop 6, Alan R. Liss, New York, NY.

Sadovnick, A.D., Armstrong, H., Rice, G.P.A., Bulman, D., Hashimoto, L., Paty, D.W., Hashimoto, S.A., Warren, S., Hader, W., Murray, T.J., Seland, T.P., Metz, L., Bell, R., Duquette, P., Gray, T., Nelson, R., Weinshenker, B., Brunet, D. and Ebers, G.C. (1993) A population-based study of multiple sclerosis in twins: update. Ann. Neurol. 33, 281–285.

Sadovnick, A.D. and Baird, P.A. (1988) The familial nature of multiple sclerosis: Age-correlated empiric recurrence risks for children and siblings of patients. Neurology 38, 990–991.

Sharief, M.K. and Thompson, E.J. (1992) In vivo relationship of tumor necrosis factor alpha to blood-brain barrier damage in patients with active multiple sclerosis. J. Neuroimmunol. 38, 27–33.

Tienari, P.J., Wikström, J., Sajantila, A., Palo, J. and Peltonen, L. (1992) Genetic susceptibility to multiple sclerosis linked to myelin basic protein gene. Lancet 340, 987–991.

The IFNβ Multiple Sclerosis Study Group (1993) Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 43, 655–661.