Monoclonal gammopathies in the adult population of Finistère, France

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SUMMARY Three hundred and thirty-four monoclonal gammopathies were detected in the sera of 30 279 adults from Finistère.

Monoclonal gammopathies (MG) are more common in Finistère than in Paris and their distribution is not homogeneous. IgG paraproteins are particularly common in the northeast of Finistère whereas IgM paraproteins are more common in the southwest. Family studies and the high degree of inbreeding would support the hypothesis that there is a genetic predisposition to develop MG but the occurrence of paraproteins among three non-consanguineous couples seems to favour the existence of an environmental factor.

A survey of sera from blood donors in Finistère showed an abnormally high frequency of monoclonal proteins¹ which was mirrored in the blood of hospital patients.² Most of the studies of monoclonal gammopathies are on selected groups of people^{3,4} such as hospital patients,² the elderly or blood donors.⁵ None of these groups is representative of a normal population.

Material and methods

In an attempt to assess the frequency of monoclonal gammopathy in a representative cross-section of the population we examined the sera of 30 279 members of the "Mutualité Sociale Agricole du Finistère" when they presented for their five-yearly health checks in 1976 and 1977.

The sample included three different groups of people. Farmers and their families made up one group of 25 326. They comprise most of the population of Finistère and many have lived in one village for more than one generation. The other two groups, 4953 in all, were made up either of staff of the Mutualité or of trades people. The members of these groups were more mobile and were less likely to be natives of Finistère. The incidence of monoclonal gammopathy was assessed in all the separate districts of the region.

The sera were identified by the surname, given name, place and date of birth. The latter was missing from 279 samples. All the samples were analysed by

semimicroelectrophoresis on cellulose acetate, using TRIS veronal buffer pH 8.8 and amido black stain. The method was sufficiently sensitive to detect less than 1 g/l of monoclonal proteins and was simple enough to allow 160 sera to be studied in 4 h. All abnormal strips were identified by immunoelectrophoresis using broad spectrum and monospecific antisera against heavy and light chains. The concentration of the immunoglobulin was measured using the Mancini technique of radial immunodiffusion. The general practitioner was asked to obtain urine for Bence-Jones protein analysis and to fill in a questionnaire on all individuals with a monoclonal protein.

STATISTICAL ANALYSIS

The frequency of MG in each group has been calculated taking age and sex into account. It will become apparent that the observed frequency of MG varies considerably not only with sex and age but also with the class of heavy chain. Hence comparison between frequencies obtained from different population groups is difficult. The global frequency should never be used because it is a function of the composition of each group. Assuming that the age and sex distribution was the same in the three groups the expected frequency of monoclonal protein was calculated as:

$$\begin{aligned} & (Nm\ 30 \times Fm\ 30 + Nf\ 30 \times Ff\ 30) + \dots \\ & (Nm\ 40 \times Fm\ 40 + Nf\ 40 \times Ff\ 40) + \dots \end{aligned}$$

where Nm 30 and Nf 30 were the number of men

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and women who were between 30 and 39 years old, and Fm and Ff were the observed monoclonal protein frequencies in that particular age group in the population of Finistère (Table 1).

The numbers of observed and expected MG were compared using the χ^2 test.

Results

INCIDENCE OF MG ACCORDING TO AGE

The frequency of MG increased with age. None occurred in a person under the age of 30 but the incidence was 4.17% in people over 80. The age distribution of heavy chains was different. IgG occurred in younger people in the age range 35 to 84 (median 66), IgM paraproteins were found over an age range of 50 to 90 (median 73).

MG AND SEX

MG was 1.6 times more frequent in men over the whole range of ages but the ratio changed from three for people in their thirties to 1.5 for people in their eighties. The sex-ratio also varied according to the heavy chain class; it was similar for IgG (1.3) and IgA (1.4) but much higher for IgM (3.2).

The risk of developing an IgM gammopathy calculated by Woolf's formula is 4.6 times higher for men than for women ($p < 0.0001$).

DISTRIBUTION OF MG ACCORDING TO CLASS AND TYPE

Table 2 shows the high frequency of IgM MG in Finistère. The low frequency (5.9%) of IgA MG in the general population contrasts markedly with the high (14.3%) frequency in hospital patients and may reflect either difficulty in detecting monoclonal bands in the α and β regions of the protein strip or a genuinely low incidence of asymptomatic monoclonal IgA paraproteins.

The frequency of light chain disease is probably artificially low as we had the opportunity to study only sera in most subjects. A diagnosis of myelomatosis was made in four of the subjects in whom light chains were detected in the serum, and two of them died of the disease less than a year after the abnormal protein was discovered.

Four double paraproteins were discovered and in addition there were two cases of heavy chain disease in 30-year-old women. Two monoclonal proteins were not identified because there was too little serum.

DISTRIBUTION OF MG IN AGRICULTURAL AND NON-AGRICULTURAL POPULATIONS

The overall frequency of MG in the agricultural population was 1.24% and looked very different from the frequency of 0.42% in the non-agricultural population (Table 3). However the difference was artificial ($p = 0.50$) and was the consequence of

Table 1 *Population and prevalence of monoclonal gammopathy in Finistère, France*

Age (yr)	Males	Females	Total
< 29	0 0/1640	0 0/1107	0 0/2747
30-39	0.20 3/1477 IgG = 3	0.06 1/1531 IgG = 1	0.13 4/3008
40-49	0.47 15/3199 IgG = 9 IgA = 2	0.23 7/3078 IgG = 6	0.35 22/6277
50-59	0.84 29/3462 IgG = 17 IgA = 3	0.59 19/3214 IgG = 14 IgM = 4	0.72 48/6676
60-69	2.09 56/2673 IgG = 37 IgA = 3 IgM = 16	1.21 39/3225 IgG = 33 IgA = 2 IgM = 4	1.61 95/5898
70-79	3.77 82/2173 IgG = 43 IgA = 5 IgM = 34	1.20 48/2501 IgG = 34 IgA = 5 IgM = 9	2.78 130/4674
> 80	5.30 15/283 IgG = 8 IgM = 6	3.43 15/437 IgG = 8 IgM = 3	4.17 30/720
Unknowns	2.07 4/193 IgG = 4	1.16 1/86 IgG = 1	1.79 5/279
Total	1.35 204/15 100	0.86 130/15 179	1.10 334/30 279

For each group, the first figure is a percentage, it is followed by the number of observed MG and the number of people tested. Underneath, we give the heavy chain class which is concerned.

Table 2 Distribution of MG according to class and type

	Heavy chain class			Light chain gammopathies	Double paraproteins and heavy chain diseases
	IgG	IgA	IgM		
Kappa	125 57.3 %	10 52.6 %	65 75.6 %	3 75 %	
Lambda	93 42.7 %	9 47.4 %	31 24.4 %	1 25 %	
Total	218 67.9 %	19 5.9 %	86 23.7 %	4 1.3 %	6 1.9 %

Table 3 Comparative frequency of the MG in farmers and the non-agricultural population

Age (yr)	Agricultural population		Non-agricultural population	
	Males	Females	Males	Females
< 29	0 *0/777	0 0/617	0 0/863	0 0/490
30-39	0-12 1/813	0-08 1/1309	0-30 2/664	0 0/222
40-49	0-51 12/2345	0-26 7/2677	0-35 3/854	0 0/401
50-59	0-86 24/2787	0-52 15/2902	0-74 5/675	1-28 4/312
60-69	2-13 53/2489	1-21 38/3145	1-63 3/184	1-25 1/80
70-79	3-80 80/2111	1-93 48/2483	3-23 2/62	0 0/18
> 80	5-56 15/270	3-45 15/435	0 0/13	0 0/2
Unknowns	2-94 3/102	1-56 1/64	1-10 1/91	0 0/22
Total	1-61 188/11 694	0-92 125/13 632	0-47 16/3406	0-32 5/1547

*The observed incidence of MG in the sample.

different age and sex distributions in the two populations.

DISTRIBUTION OF MG ACCORDING TO CLINICAL SYMPTOMATOLOGY

Only 111 answers to the questionnaire were correctly filled in and included clinical, radiological, and chemical data.

From the data available (Table 4) it was estimated that 22.5% of the MG were associated with a malignant immunoproliferative disease (myelomatosis, Waldenström's macroglobulinaemia, chronic lymphatic leukaemia). The prognosis of subjects with IgM and particularly with IgA paraproteins appeared worse than those with IgG paraproteins. 18.9% of monoclonal proteins were linked to chronic infection, cirrhosis, cancer or autoimmune disease. 54.1% could be classified as asymptomatic when the abnormal protein was detected. Five cases were unclassifiable because they had signs of undefinable malignancy. 17.1% of IgG, 30.2% of IgM and 47.4% of IgA monoclonal gammopathies were associated with immune deficiency, proportions similar to those in clinical disease.

GEOGRAPHICAL DISTRIBUTION OF MG WITHIN THE REGION

The distribution of MG was not homogeneous. As shown on the map, there were two areas in which there was an excess of IgG MG, the larger one in the northeast of Finistère near Morlaix. Here there were 79 IgG MG in 8453 sera tested; taking account of the age and sex of the population tested, only 62.5 would be expected ($p < 0.01$). In the smaller area in the southeast of the region there were 15 IgG MG in 1189 sera tested when only 6.8 would be expected ($p < 0.01$).

There were two areas in which there was an excess of IgM MG: one in southwest Brittany where there were 19 in 3269 subjects when only 10.7 were expected ($p < 0.01$) and another smaller area in the northwest where there were nine in 1506 subjects and only 2.6 were expected ($p < 0.001$).

Discussion

Our results confirm those of others and show that the frequency of MG depends on age^{3 4 6 7} and sex.^{5 6 8} However in our population the distribution of

Table 4 Disorders associated with MG according to the 111 answers of our questionnaire

Aetiology	IgG	IgM	IgA	Light chains	Double paraproteins	Total
Asymptomatic	61.4 (43)	43.3 (13)	50.0 (4)	—	—	54.1 (60)
Chronic infection	8.6 (6)	3.3 (1)	12.5 (1)	—	—	7.2 (8)
Cirrhosis	4.3 (3)	10.0 (3)	—	—	—	5.4 (6)
Rheumatoid arthritis	4.3 (3)	—	—	—	—	3.6 (4)
Cancer	2.9 (2)	3.3 (1)	—	—	—	2.7 (3)
Chronic lymphatic leukaemia	—	3.3 (1)	—	—	—	0.9 (1)
Myelomatosis	14.3 (10)	—	25.0 (2)	100.0 (2)	—	12.6 (14)
Waldenström's macroglobulinaemia	—	33.3 (10)	—	—	—	9.0 (10)
Atypical symptoms	4.3 (3)	3.3 (1)	12.5 (1)	—	—	4.5 (5)
Total	70	30	8	2	1	111

class and type of immunoglobulin differs from those of other large series⁹⁻¹³ and observed frequencies are a function of the class of heavy chains.

It is difficult to compare results from different populations because of variation of these parameters (age, sex and heavy chains): however an

attempt at comparison is useful in analysing the influence of genetic and environmental factors in relation to MG. The comparison of overall frequency which is made in most published series gives misleading results. We analysed the results of Axelsson,⁶ Kyle¹⁴ and Fine⁵ by our technique. In Axelsson's series there were 64 MG whereas 68.8 would be expected. His sample seems similar to ours except for IgA and IgM distribution. Kyle detected 15 MG in 1200 subjects whereas, using our computation, 20.7 would be expected; the difference is not significant. However Fine, in Paris, found only 10 MG in 6401 subjects whereas we should have expected 20; a significant difference ($p < 0.01$). Hence MG are twice as frequent in Finistère as they are in Paris, an observation which supports that of Milham¹⁵ who found that MG are more common in agricultural populations. We, however, found no significant difference between the two social and economic categories.

The role of genetic factors has been invoked^{16 17} and could explain the observed areas of high frequency of the disease.^{14 18-21} In favour of these reports in relation to our results the population of Finistère and especially of Trégor Finistérien and Pays Bigouden is known to be highly inbred. In an earlier survey 81.8% of 14 596 subjects were born of two parents who themselves were born in the same area. In addition the 111 answers to our enquiry revealed 13 familial cases of MG, a not uncommon finding.²²⁻²⁶

Several environmental factors have been evoked. Natural or accidental irradiation²⁷⁻³⁰ as a harmful effect seems to be well supported, and it is significant that there is high natural radioactivity in Brittany. However we have shown that the areas of high MG

Map of Finistère

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frequency seem to correspond only very approximately with the uranium-rich granite areas. The role of this factor deserves to be studied in greater depth in view of Court-Brown's work³¹ showing a higher frequency of malignant haemopathies among the inhabitants of granite houses, which are common in Finistère. Like Kyle³² we have observed three couples (husband and wife) with MG. No consanguinity could be traced and in one case the man was not even Breton. It could be suggested that identical environmental conditions provoked similar dysimmunities in both spouses. Were this hypothesis correct the cases observed within the same family would not necessarily be the consequence of genetic predisposition as all the subjects live in the same environment.

Finally, the difference in incidence of MG in Paris and Finistère could mean that the rural population are more affected than townspeople because they are exposed to stimulation by heteroantigens (virus, rickettsia, etc.). This would support the observations of Milham;¹⁵ however the incidence of MG associated with chronic infection is similar in other series.

Despite the interpretational difficulties of the investigation of a pathology which is very probably multifactorial it would be of interest to undertake statistical studies in widely differing areas in order to analyse the role of the various aetiological factors.

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References

- Saleun JP, Baret M. Paraprotéines monoclonales chez les donneurs de sang du Finistère. *Revue Française de Transfusion* 1974;17,4:349-59.
- Youinou P, Le Goff P, Saleun JP, Jouquan J, Tymen G, Le Menn P. Les gammopathies monoclonales (revue critique de 219 dossiers colligés en 3 ans). *Pathol Biol (Paris)* 1977;25,8:517-21.
- Derycke L, Fine JM, Boffa GA. Dysglobulinémies essentielles chez les sujets âgés. *Nouv Rev Fr Hematol* 1965;5:729-38.
- Hallen J. Frequency of abnormal serum globulins (M components) in aged. *Acta Med Scand* 1963;173,6:737-44.
- Fine JM, Lambin P, Le Roux P. Frequency of monoclonal gammopathy (M components) in 13,400 sera from blood donors. *Vox Sang* 1971;23,4:336-43.
- Axelsson U, Bachmann R, Hallen J. Frequency of pathological proteins (M Components) in 6,995 sera from an adult population. *Acta Med Scand* 1966;179,2:235-47.
- Clauvel JP, Danon F, Seligmann M. Immunoglobulines monoclonales décelées en l'absence de myélomes ou de macroglobulinémies de Waldenström. *Nouv Rev Fr Hematol* 1971;11:677-88.
- Martin NH. The incidence of myelomatosis. *Lancet* 1961; i:237.
- Creysse R, Gibaud A, Cordier JP, Boissel JP. The frequency distribution of heavy chain classes and light chain types of 1,000 monoclonal immunoglobulins. *Biomedicine* 1975;22:41-8.
- Fateh-Moghadam A, Lamerz R, Knedel M, Tsimbas B. Electrophoretische Klassen und gruppen Verteilung von Paraprotein und normalen Immunoglobulinen. *Klin Wochenschr* 1971;8:458-67.
- Fine JM, Lambin P. Distribution of heavy chain classes and light chain types in 757 cases of monoclonal gammopathies. *Biomedicine* 1975;22:323-7.
- Obderhofer A, Schnauffer K, Lange HJ, Neiss A. Zur Verteilung von Paraproteinämien nach Geschlecht und Alter der Patienten, paraprotein Klassen, subklassen und leichtketten typen. *Zeitschrift für Klinische Chemie und Klinische Biochemie* 1973;196,5:361-7.
- Ossermann EF, Takat Suki K. Plasma cell myeloma—gammaglobulins synthesis and structure. *Medicine* 1963; 42:357-84.
- Kyle RA, Finkelstein S, Elve Bach LR, Jurland LT. Incidence of monoclonal proteins in a Minnesota Community with a cluster of multiple myeloma. *Blood* 1972;40,5:719-33.
- Milham S. Leukemia and multiple myeloma in farmers. *Am J Epidemiol* 1971;94,4:307-10.
- Seligmann M. Genetic predisposition to Waldenström's macroglobulinemia. *Acta Med Scand [Suppl]* 1966; 445:139-40.
- Spengler GA, Butler R, Fischer C, Ryssel HJ, Schmidt E, Siebner H. On the question of familial occurrence of paraproteinemia. *Herv Med Act* 1966;33:208-19.
- Dawson AA, Ogston D. High incidence of myelomatosis in north east Scotland. *Scott Med J* 1973;18,3:75-7.
- Kyle RA, Nobrega FT, Kurland LT. Multiple myeloma in homestead country Minnesota 1945-1964. *Blood* 1969; 33,5:739-45.
- Stalsberg H. Lymphoreticular tumors in Norway and in other countries. *J Natl Cancer Inst* 1973;50,6:1685-702.
- Sutter J, Tabah L. Fréquence et répartition des mariages consanguins en France. *Population* 1948;3:607-30.
- Fine JM, Lambin P, Valentin L, Blatrix Ch. IgG monoclonal gammopathy in the sister of a patient with Waldenström macroglobulinemia. *Biomedicine* 1973; 19:117-21.
- Meijers KAE, De Leeuw B, Woormolen-Kalova M. The multiple occurrence of myeloma and asymptomatic proteinemia within one family. *Clin Exp Immunol* 1972; 12,2:185-93.
- Odeberg LM, Jahansson BG, Berlin SO. Immunoglobulin analysis in families of myeloma patients. *Acta Med Scand* 1974;196,5:361-5.
- Seligmann M, Danon F, Mihaesco C, Fudenberg HH. Immunoglobulin abnormalities in families of patients with Waldenström macroglobulinemia. *Am J Med* 1967; 43:66-83.
- Williams AC, Erickson JL, Polesky HF, Swain WT. Studies of monoclonal immunoglobulins (M components), in various Kindreds. *Ann Intern Med* 1967;67, 2:309-27.
- Anderson RE, Ishida K, Li Y, Ishimaru T, Nishiyama H. Geographic aspects of malignant lymphoma and multiple myeloma. *Am J Pathol* 1970;61,1:85-97.
- Lewis EA. Leukemia, multiple myeloma and aplastic anemias, in American radiologist. *Science* 1963;142: 1492-4.
- Lilienfeld AM. Epidemiological studies of the leukemologic effects of radiations. *Yale J Biol Med* 1966;39: 143-4.
- Nishiyama H, Anderson RE, Ishimaru T, Ishida K,

- Li Y, Okabe N. The incidence of malignant lymphoma and multiple myeloma in Hiroshima and Nagasaki atomic bomb survivors. *Cancer* 1973;6:1301-9.
- ³¹ Court-Brown WM, Doll R, Spiers FW, Duffy BJ, Mac-Hugh MT. Geographical variations in leukemia mortality in relation to background radiations and other factors. *Br Med J* 1977;i:1753-9.
- ³² Kyle RA, Heath CW, Carbone P. Multiple myeloma in spouses. *Arch Intern Med* 1971;71:944-6.

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