INDIVIDUAL STUDY

Paraproteinaemia in general practice

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Since 1963, we have seen 18 adults with paraproteinaemia. These are from a three-man private practice. As we cannot keep an age-sex register I am unable to state an incidence but the practice is not unusual in its structure and closely follows the pattern of the area (Colling, 1963).

There is no population study of the condition in this country and only in Sweden is there a relevant study of its incidence. An exploratory study was carried out by Axelsson *et al.* (1966) who found paraproteins in 0·9 per cent of 6,995 sera from an adult population of a small town in southern Sweden. This covered 70 per cent of the population over 25 years of age. There were 64 adults (36 males and 28 females). A malignant condition was found in only four; the frequency of this finding rose subsequently with age, reaching 5·7 per cent of the age group 80–89.

Hobbs from his Postgraduate Hospital Survey (1967) produced a different story in a highly selected group. He found 55 patients from routine electrophoresis of sera from 7,200 new patients. After three years' follow up only 40 per cent could be considered to have a benign condition, a malignant condition being diagnosed in 53 per cent. The diagnosis was uncertain in seven per cent.

Definition

Paraproteins are those serum proteins which on electrophoresis are found to run as an abnormal band between the positions occupied by the β and post γ protein fractions. They are proteins closely related physically and electrically to normal γ globulins but lack antibody specificity.

Method

The sera were examined with paper electrophoresis using standard laboratory techniques. Results were verified on at least two separate occasions.

Results

The age and sex distribution is shown in Figure 1. There were 11 men and seven women with ages ranging from 45 to 89 years.

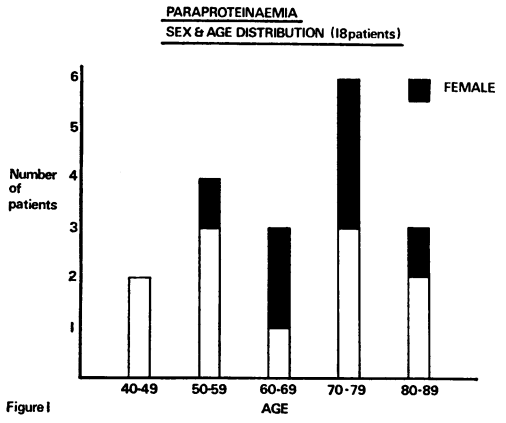

Figure 1. Paraproteinaemia

The annual incidence is shown in Figure 2. Apart from two fallow years the incidence

has been approximately constant. Though considered a condition of old age, one third of our patients were less than 56 years old and of this group of six, five were male.

1964	1965	1966	1967	1968	1969	1970
3	1	0	4	3	3	4

Figure 2. Paraproteinaemia: annual incidence

The series can be classified into the following groups:

		Cases	*Deaths*
(1) Malignant	Myelomatosis	4	4
	Waldenström's macro-globulinaemia	1	1
(2) Benign		3	0
(3) Undefined		10	4

Three cases of myelomatosis satisfy all the criteria of diagnosis, with paraproteinaemia, marrow changes with excessive plasma cells and widespread osteolytic lesions. The fourth had paraproteinaemia and marrow changes but skeletal x-rays were not done.

Patient 1. A 65 year-old spinster presented in January 1963 with a six week history of anorexia and abdominal pain. The abnormalities were a normochromic anaemia of 10·2 g., ESR 122 mm/hour (Westergren), gross disturbance of serum proteins with reversed albumin/globulin ratio and a paraprotein in the gamma globulin zone. She was referred to the Royal Victoria Infirmary, Newcastle-upon-Tyne. Tests including marrow biopsy confirmed the diagnosis. There was no Bence–Jones proteinuria. She was not x-rayed, and for 15 months remained well though the serological changes were unaltered. In August 1964, she began having bone pains and her general condition rapidly worsened. The haemoglobin dropped and Bence–Jones protein appeared in the urine. She had a raised blood urea and within two weeks was dead from renal failure. At necropsy there was terminal bronchopneumonia, widespread skeletal myeloma deposits, and both kidneys pale and swollen. Microscopically the tubules were full of myeloma protein.

Waldenström's macroglobulinaemia is diagnosed on the following criteria: (i) severe lassitude with anaemia and neutropenia; (ii) bleeding without thrombocytopenia or clotting defect; (iii) mild splenomegaly and slight generalised lymphadenopathy; (iv) biopsy evidence, with lymph nodes or marrow infiltrated with atypical lymphoid cells; (v)IgM paraprotein.

Patient 4. In 1965, an 81 year-old shoe repairer had a mild stroke. At that time he was found to have a raised ESR (50 mm/hour, Westergren). He made a good recovery and was not seen for another three years. He then presented with profuse epistaxes requiring hospital treatment. He had not been well for the previous few months and it was found that he had lost weight and had still a raised ESR. Serum electrophoresis and immunoelectrophoresis showed an IgM paraprotein. He gradually ebbed over the next eight months; he became anaemic with a neutropenia and bleeding diathesis. There was generalised lymphadenopathy but no enlargement of liver or spleen. Terminal hospital investigations showed right lung consolidation. He did not respond to antibiotics and died after two days of confusion, stupor and coma. A necropsy was not done. This patient had four of the five features: lymph nodes and marrow were not examined.

Benign group (three patients)

I have defined the benign group by Hobbs' (1967) criteria: (i) no symptoms related to paraprotein; (ii) no palpable enlargement of the lymph nodes, liver or spleen; (iii) negative radiological survey; (iv) apparently normal bone marrow; (v) followed for at least three years and no detectable change in the overall picture.

Patient 10 is typical of this group which satisfy all the benign criteria. This man was 66 when the paraprotein was found in 1964. He had a 25-year history of ischaemic heart disease and, after being seen by a cardiologist in 1961, was started on longterm anticoagulant treatment (phenindione). The prothrombin level was maintained at therapeutic levels on a virtually unchanged dose for three years, when, two weeks after a completely satisfactory routine test, he had sudden haematuria. The prothrombin level was now abnormally low and on stopping treatment and giving vitamin K1, returned to normal. There was no explanation for the change and looking for a cause he was found to have a very

high ESR 90 mm/hour, Westergren) and a discrete band in the gamma globulin range. (1·4 g per 100 ml.). Bone marrow and skeletal x-rays were normal. He remains well but there has been no change in paraprotein level or ESR.

Undefined (ten patients)

Three were dead from cancer within five months of the paraprotein findings.

Pattent 6. This 79-year old man had been unwell for more than 18 months. In July 1968, at the time of a urinary infection he was found to have a raised ESR (80 mm/hour, Westergren) and a subsequent electrophoresis revealed a gamma paraprotein (1·26 g per 100 ml.). Five months later, and after the finding of an enlarged hard liver, a laparotomy was done. It was impossible to identify a primary growth but an epigastric lymph node was removed for histological examination. It was infiltrated with adenocarcinoma. On the third post-operative day, he collapsed and died from a probable pulmonary embolism. Permission for necropsy was refused.

One patient died from pneumonia and congestive heart failure 18 months after the discovery of paraproteinaemia.

Another is well two years after the finding and waits to be included in the benign group.

The remaining five patients were all diagnosed in the past year and it is therefore much too soon to classify them as benign. Four were so well that it was felt there was no justification for carrying out further investigations, though it is realised that this attitude could be easily challenged. All patients with paraproteinaemia are seen for clinical and serological evaluation at least every six months.

In the benign and undefined groups (13 cases) the principal feature prompting electrophoresis of serum is shown in Figure 2.

Raised ESR (higher than 40 mm/hour)	5
Recurrent infections	2
Cancer	2
Unexplained proteinuria	1
Previous history of pneumococcal meningitis	1
Chance	2

The following is a good example of this undefined group and illustrates the importance of suspicion in diagnosis.

Patient 16. This 45 year-old man was first seen in March 1970 when he was found to have severe essential hypertension. His previous history was significant in that he had proven pneumococcal meningitis in 1950. As this condition is associated with disturbed immunity, his serum proteins were screened. He had a paraprotein band in the gamma fraction (1·3 g per 100 ml.) and an increased number of plasma cells in the marrow. There was no anaemia, rise in ESR or skeletal changes. He is well and his hypertension is controlled by methyldopa.

Discussion

The finding of paraprotein points to a profound disturbance of immunological synthesis. Between the β and post γ protein fractions on electrophoresis, is an area of great interest, excitement and speculation. This is the zone of gamma globulins and concerned with humoral immunity. These immunoglobulins not only protect the body from bacteria and toxins but may have an important place in auto-immunity and the pathogenesis of cancer and ageing.

In the 13 cases constituting the bening and undefined groups a raised ESR was responsible for the paraprotein finding in five. Lane (1970) suggested that many cases of paraproteinaemia could be detected earlier by electrophoresis on blood samples with an ESR of over 50 mm/hour. Recurrent infections, especially of the urinary and respiratory tract, are more common in patients with paraproteinaemia. Similarly the discovery or history of an unusual infection raises suspicion of disordered immunity and the need to exclude immunological deficiency.

Screening of immunoglobulins is therefore not merely of academic interest. Patients with paraproteinaemia are at risk and perhaps something can be done to anticipate or redress the effects of their quantitative or functional deficiency.

By following the 'non-malignant' groups, it is possible to spot the early changes of myelomatosis. This is worthwhile now there is a possibility of treatment with cytotoxic drugs.

The isolated finding of paraprotein is not necessarily of grave significance. In this study, admittedly selective, only five cases were associated with myelomatosis and Waldenström's

macroglobulinaemia. In their population survey, Axelsson and Hällén (1968) found that benign paraproteinaemia was 40–50 times more common than myelomatosis and Waldenström's macroglobulinaemia. Paraproteins can occur, but are uncommon, in lymphosarcoma and chronic lymphatic leukaemia. For example, Hobbs (1967) found that lymphomas accounted for only eight out of the 223 malignant conditions. In this series there were three cases associated with cancer. Though paraproteins are found in company with cancers their frequency is said to be no greater than would be expected by chance. (Hällén, 1966; Hobbs, 1967).

These figures show that paraproteinaemia is a relatively common finding in general practice. As a comparison, we saw during the same period seven patients with bronchial cancer and nine with thyrotoxicosis.

I suggest protein examination would repay study either from general practice itself or better still from a well planned population survey along the lines of Axelsson's Swedish investigation.

Summary

Eighteen patients with paraproteinaemia were seen in a general practice in the last seven years. In five there was an association with malignancy of the reticulo-endothelial system. In the remainder there is a group, which by contrast and definition, can be classified as benign. It is emphasized that individuals with an unexplained raised ESR, frequent or unusual infections, should be screened by electrophoresis of their serum proteins. This estimation would be of clinical and epidemiological interest and it is suggested that a population study would be valuable.

Acknowledgement

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USE OF A COMPUTER IN GENERAL PRACTICE

A five week experiment in January 1970 enabled a general practitioner in Exeter using a visual display unit to access a computer in Croydon through a telephone line during consultation.

The computer allowed streamlined medical record construction and amendment, rapid storage and retrieval, and automatic selection of records by common component. The new synoptic record format disposed data for quick clear appraisal, so that disease recurrence, association and progression were highlighted.

Legibility, system reliability, obviation of record handling procedures, and economy of record accommodation space were further advantages.

An integrated patient record compiled from all sources, and terminal intercommunication would be achieved by a multiple terminal system.

Preece, J. F., Gillings, D. B., Lippmann, E. D. & Pearson, N. C. (1970). An on-line record maintenance and retrieval system in general practice, *Biomedical Computing*, **1**, 329–337.