

probably desynchronized vis-a-vis some of the other clocks controlling circadian rhythms of hormone release and urinary excretion.

Some workers^{8,9} have suggested that normal mammalian and avian circadian rhythms may result from the locking together of two 12-hour rhythms, one entrained to dawns, the other to dusks, which can be separated under certain experimental conditions. This may have relevance for human disease.

The depressive phase of our patients may therefore be characterised physiologically as one of temperature-clock desynchronisation. The short-term desynchronisation of human circadian rhythms produced by east-west and west-east flight is experienced partly as a dysphoria, and perhaps the subjective unpleasantness of depressive illness is partly the awareness of desynchronisation. Electric convulsion therapy could be regarded as a powerful external synchroniser; would it be therapeutically equivalent if given always at midnight, or randomly at any hour instead of (commonly) always between 0900 and 1200? Sufferers from depressive illness are often unable to work, particularly in the mornings, while in normal people work performance and body temperature are closely correlated.⁵ We have some preliminary results with card-sorting as a test of performance suggesting that this correlation will hold also for depressed people and that performance drops in parallel with temperature during the morning in the depressed.

Possibly these six subjects, although their earlier histories, symptom-pictures, and drug responses in no way distinguish them, may represent only some rare clinical subgroup and not be typical of manic-depressive patients in general. Even normal people may differ constitutionally in their overall circadian pattern—for example, the morning people and evening people of Kleitman.³ It is necessary to examine many more people, not only depressives but other categories, and to look not only at temperature and performance tests but also at rhythms of

hormones¹⁰ and urinary electrolytes.¹¹ Halberg¹² has suggested that the rhythm of recurrence of manic-depressive episodes may be determined by the extent to which two circadian rhythms are out of phase.

Our observations of a reversible abnormality of daily temperature cycle during depressive episodes support the hypothesis that manic-depression is the manifestation of disordered circadian rhythms and suggest this as a potentially fruitful approach to the pathology of mental illness.

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Polyarthritis in adults with hypogammaglobulinaemia and its rapid response to immunoglobulin treatment

A D B WEBSTER, G LOEWI, R D DOURMASHKIN, D N GOLDING, D J WARD, G L ASHERSON

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Summary

Five patients with primary hypogammaglobulinaemia developed a severe polyarthritis that had some features in common with rheumatoid arthritis. Their joint disease could be distinguished from rheumatoid arthritis, however, by the dramatic improvement after gamma-globulin treatment. The arthritis of hypogammaglobu-

linaemia can, therefore, be included among the few potentially curable polyarthritides.

Introduction

The association of non-septic arthritis and primary hypogammaglobulinaemia was first described in children.¹ Others have subsequently described the association in both children and adults and some authors have regarded the pathogenesis of the joint disease as identical to that of classical rheumatoid arthritis.² We have studied five adults with primary hypogammaglobulinaemia and polyarthritis and have attempted to distinguish their disease from rheumatoid arthritis. The most clear-cut difference is that the arthritis in patients with hypogammaglobulinaemia improved rapidly after gammaglobulin replacement therapy.

Patients

The five patients all developed recurrent infections as adults and were classified as having adult onset "variable" primary hypogammaglobulinaemia.³

Clinical Research Centre, Harrow, Middlesex HA1 3UJ

A D B WEBSTER, MRCP, consultant physician
G LOEWI, DM, FRCPATH, consultant pathologist
R D DOURMASHKIN, DM, head of section of electron microscopy
G L ASHERSON, FRCP, FRCPATH, head of division of immunology

Princess Alexander Hospital, Harlow, Essex CM20 1QX

D N GOLDING, FRCP, consultant rheumatologist

Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, Shropshire SY10 7AG

D J WARD, MRCP, consultant rheumatologist

Case 1—Recurrent infections started in this man when he was 44. In February 1974, when he was 47, he was found to have slight swelling of the metacarpal-phalangeal (MCP) joints of the right hand; stiff wrists, allowing only 60° flexion; bilateral olecranon bursitis, knee effusions, and ankle swelling; and tenosynovitis of dorsal tendon sheaths of both feet and the right hand. He also had recurrent bronchitis, and a benign spindle cell thymoma was removed in April 1974. In November he started gammaglobulin treatment, which produced a dramatic improvement in joint symptoms within one week. He returned to work a month later, having been absent for one year. Eleven months after the start of treatment he still had dorsal tenosynovitis of the tendon sheaths of both feet, but all other joints were quiescent.

Case 2—This woman was examined in March 1974, when she was 31, and found to have bilateral knee effusions and stiff painful wrists and MCP joints. She had had recurrent infections since she was 25 and had had lobectomy for bronchiectasis when she was 29. She also had generalised lymphadenopathy (a lymph node biopsy showed reactive hyperplasia), which is a rare complication of hypogammaglobulinaemia, and splenomegaly, which is a common complication. Gammaglobulin treatment, started in October 1974, produced a dramatic improvement in joint symptoms within two weeks; no symptoms remained after 12 weeks. She was followed up for 17 months.

Case 3—In February 1970, when she was 34, this woman was found to have a swollen right wrist; stiff shoulders and hips; tenosynovitis of the dorsal tendon sheaths of the right hand; and left knee effusions. Gold therapy produced some improvement, but in 1972 synovectomy of the dorsal tendon sheaths of the right hand was performed and many rice bodies removed. She had had recurrent infections since she was 13, and she had undergone right left lower lobectomy when she was 32. Treatment with gammaglobulin, started in April 1972, produced improvement within four weeks in all joints except the left knee, which continued to swell periodically during the follow-up period of 3 years 7 months. When she was 36 she underwent right middle lobe lobectomy, and a year later chronic haemorrhagic cystitis was diagnosed and responded to steroids and tetracycline. The sicca syndrome, with deficient vaginal and conjunctival secretions, was diagnosed when she was 37.

Case 4—Recurrent infections started in this patient when she was 19. She had received gammaglobulin before, from the age of 26 to 31 and from the age of 32 to 38. Both times treatment had been withdrawn because of anaphylactic reactions. When examined in April 1975, at the age of 39, she had stiff shoulders, elbows, and MCP joints of hands; stiff knees with right patella bursitis; and tenosynovitis of flexor and extensor tendons in wrists. She also had splenomegaly and chronic bronchitis. Further gammaglobulin treatment, started in May 1975, produced a gradual improvement over six months, although stiffness of the shoulders remained and she developed left olecranon bursitis five months after treatment. Additional treatment for a further two months with regular plasma infusions produced complete recovery. This patient was followed-up for nine months.

Case 5—This man started to suffer from recurrent infections when he was 20 years old. He received gammaglobulin when he was 34, and treatment continued until June 1969 (age 49), when it was discontinued owing to severe anaphylactic reactions. When examined in September 1969 he had stiffness in shoulders, ankles, and wrists and bilateral knee effusions. He had an ulnar nodule; histological examination showed a fibrinoid lattice in an oedematous acellular nodule with no cellular necrosis. This patient also had splenomegaly, x-ray evidence of bilateral basal bronchiectasis, and generalised lymphadenopathy. He refused further gammaglobulin, but the joint symptoms improved after a course of regular plasma treatment. Plasma therapy has been continued for the past four years, and the joint disease has remained inactive.

The polyarthritides in these patients generally spared the small joints of the hands, and no bony erosions were seen on radiographs of the hands and knees in any patient. Recurrent severe reactions to gammaglobulin injections are rare in hypogammaglobulinaemia, but two patients (cases 4 and 5) had discontinued their injections because of them.

Gammaglobulin treatment—The four patients who received gammaglobulin replacement treatment after examination and were followed up were given a five-day loading course of gammaglobulin (Lister Institute) of 50 mg/kg body weight/day followed by weekly maintenance injections of 25 mg/kg.

Methods

Serum immunoglobulin levels were measured in these patients at their examination by a modified Mancini method, as recommended by Rowe *et al.*⁴ Circulating T lymphocytes were recognised by their ability to bind sheep red cells and B lymphocytes were recognised by surface staining with fluoresceinated antihuman gammaglobulin (Behringwerke). Lymphocyte transformation to phytohaemagglutinin (PHA) was measured using a micromethod.⁵ Delayed hypersensitivity skin tests were performed using an intradermal injection of 0.1 ml *Candida albicans* (0.33% Bencard), purified protein derivative of tuberculin (PPD), 10 and 100 units (Ministry of Agriculture, Weybridge), and mumps antigen (Lederle). Contact sensitivity to dinitrochlorobenzene (DNCB) was assessed by sensitising the patient with 0.1 ml of a 5% solution in acetone and challenging with a 0.1% solution seven days later.

Joint effusions were aspirated in three cases and the fluids were centrifuged after a short incubation with hyaluronidase (38 U/ml). The cells were counted and cytocentrifuge preparations were examined. Fluids were kept at -70°C for complement studies. Complement activation (CH₅₀) was measured by a standard method. C3 and C4 were measured by radial immunodiffusion. Split products of C3 and C5 were identified by Laurell (rocket) electrophoresis. Biopsy specimens were obtained surgically in three cases and by needle in one case. Snap-frozen sections from one patient were stained with fluorescein-conjugated anti-immunoglobulin (Burroughs Wellcome). Effusion cells were examined for B cells by staining with fluorescent anti-immunoglobulin and for T cells by the sheep cell rosette method.

Joint fluids from two patients (cases 1 and 4) were investigated for the presence of viruses by inoculation on to the following cell lines: human diploid fibroblasts (MRC 5), secondary monkey kidney (MK), and Ohio HeLa (carcinoma of cervix). Snap-frozen synovial membranes from two patients (cases 1 and 3) were also treated with rabbit anti-rubella antibody, followed by fluoresceinated anti-rabbit globulin. A positive control was provided by infected tissue culture cells. Joint fluids from four patients were sent for routine bacteriological culture of aerobic and anaerobic bacteria and were also inoculated into Hayflicks medium for mycoplasma.

Immunological investigations of patients with arthritis. Figures in parentheses indicate 95% range of normal values

Case No.:	1	2	3	4	5*
Serum immunoglobulins (g/l):					
IgG (6.46 - 14.84)	0.5	<0.05	0.07	0.03	<0.1
IgA (0.73 - 5.52)	0.0045	<0.02	<0.001	<0.001	<0.02
IgM (0.5 - 2.61)	0.1	0.09	0.05	0.1	0.04
Circulating lymphocytes ($\times 10^9/l$)	1.936	1.440	1.008	1.824	0.928
% T lymphocytes (50-74)	69	60	68	51	ND
% B lymphocytes (11-19)	3	21	2	2	ND
Blood lymphocyte transformation to PHA cpm/10 ⁶ initial cells (4000-10 000)	11 409	3781	4961	378	ND
Delayed hypersensitivity skin tests:					
Candida	-	ND	+	ND	-
Mumps	+	ND	-	ND	-
PPD	-	ND	ND	ND	ND
DNCB	+	ND	+	ND	-
Total cell count in joint fluid cells/l ($\times 10^9/l$)	2	1	1	5	9
% Mononuclear	60	80	100	68	5
% Polymorphs	40	20		19	95
% T lymphocytes	41	15	ND	ND	ND
% B lymphocytes	3	2	ND	ND	3
Complement (CH ₅₀)	1/64	1/128	ND	1/16	ND
	C3 = 0.81 g/l (albumin 23 g/l), no split products of C3 or C5			C3 = 0.54 g/l C4 111% of normal serum (albumin 20 g/l), no split products of C3 or C5	

*Mycoplasma isolated from joint.
ND = Not done.

For electron microscopy the joint fluids were treated with hyaluronidase and then centrifuged at 3000 *g* for 15 minutes. Supernatants were then further centrifuged at 100 000 *g* for 60 minutes. The resulting pellets were fixed in buffered formaldehyde-glutaraldehyde followed by osmium, and embedded and sectioned for electron-microscopy. Similar pellets were also resuspended in a little distilled water and negatively stained with sodium phosphotungstate.

Results

The table summarises the immunological and rheumatological findings in the five patients. All patients had severe panhypogammaglobulinaemia. Three patients had lymphopenia and three had grossly depressed numbers of circulating B lymphocytes. Lymphocyte transformation to PHA was depressed in two patients, a finding which occurs in about a third of all patients with adult onset hypogammaglobulinaemia.

Four of the patients had relatively few joint fluid cells in comparison to the number usually found in patients with classical rheumatoid arthritis. Mononuclear cells predominated in four patients, and many polymorphs were seen only in one patient (case 5), in whom a mycoplasma was isolated from the joint fluid. Furthermore, in the three patients examined there were few cells showing surface staining for immunoglobulin. T lymphocytes were found in both of the two patients examined but the numbers of B and T cells together amounted only to 17% and 44% in cases 1 and 2 respectively. Joint fluids from three patients were examined for complement activity but only one (case 4) had a CH₅₀ complement level lower than that found in the serum. C3 levels were normal and split products of C3 and C5 were not found in the joint fluids from two of these patients. The latex test for rheumatoid factor was negative in three joint fluids examined and in the sera of all five patients. The Rose-Waaler test also gave negative results in all patients, and none had antinuclear factor or autoantibodies to thyroid or stomach antigens.

Virus cultures were negative and rubella virus was not identified in the synovium from two patients by an immunofluorescent technique. There was also no electron microscopic evidence of viruses. Bodies compatible with mycoplasma were seen by electron microscopy in the joint fluid of one patient (case 1). No bacteria were isolated from any patient, but *Mycoplasma pneumoniae* was isolated from the joint fluid of one patient (case 5).

Synovial biopsies were examined from four patients. All showed hyperplasia of synovial lining cells and underlying stroma. They contained increased numbers of mononuclear cells with a small proportion of polymorphs and the occasional mast cell. Vascularity was increased. The cells consisted of lymphocytes, macrophages, and fibroblasts, but no plasma cells were seen in any section in spite of a careful search of multiple sections taken from each specimen. A few deposits of haemosiderin, indicating haemorrhage, were found. The picture was one of chronic inflammation without specific features.

Discussion

We have described the association of a characteristic form of polyarthritis and adult onset hypogammaglobulinaemia. This polyarthritis predominantly affects large joints and spares fingers and toes, although teno-synovitis of the hands and feet occurs. It is non-deforming and the patients do not develop subcutaneous nodules with a classical rheumatoid histology. The patients lack rheumatoid factor and the joint effusions contain few polymorphs and have normal complement levels. The most striking feature is the response to immunoglobulin treatment. This pattern of disease will be referred to as the "arthritis of hypogammaglobulinaemia" without prejudicing its relation to other forms of arthritis.

Patients with late onset hypogammaglobulinaemia commonly develop malabsorption caused by giardiasis or possible bacterial overgrowth.⁶ The arthritis described here is probably not secondary to gut disease, however, as none of these patients had a raised faecal fat excretion. Nevertheless, a few cases of Whipple's disease with arthritis and hypogammaglobulinaemia have been reported. Cochran *et al*⁷ described such a patient who also had subcutaneous nodules which histologically were compatible with classical rheumatoid arthritis.

Is the arthritis of hypogammaglobulinaemia the same as classical rheumatoid arthritis modified by the failure of the patients to produce antibodies? There are several distinguishing features, including the absence of rheumatoid factor and erosions together with the paucity of polymorphs and normal complement levels in the joint effusions.⁸ These features may all be secondary to the failure of antibody production, however, and may not indicate fundamental differences. Nevertheless, the dramatic response to immunoglobulin treatment does distinguish these two forms of arthritis. Rheumatoid arthritis does not respond to such treatment,⁹ which suggests that the aetiology of the two diseases is different and that the arthritis of hypogammaglobulinaemia is due to an organism or toxin which is neutralised by the injected antibody.

Other forms of arthritis also occur in hypogammaglobulinaemia. Good *et al*² described a patient with hypogammaglobulinaemia and destructive joint changes who may have had classical rheumatoid arthritis. Septic arthritis also occurs in these patients and sometimes affects more than one joint. Children with primary hypogammaglobulinaemia may develop a monoarthritis or polyarthritis, often affecting the knee joints, which may run a chronic relapsing course over several years but which usually remits permanently in adolescence. We are aware of three children who have suffered with this complication.

Polyarthritis may also be associated with a dermatomyositis which occurs as a rare complication of sex-linked hypogammaglobulinaemia. The aetiology of this condition is probably related to a chronic virus infection, an echo 11 virus being isolated from one of our patients.

Our own data does indicate a raised incidence of polyarthritis in adult patients with hypogammaglobulinaemia since three of the patients described here were drawn from a population of 70 patients. This confirms the findings of Lawrence¹⁰ but is not entirely in accordance with those of McLaughlin *et al*,¹¹ who found only one case among 35 patients, although most of these were children. Nevertheless, none of these more recent reports confirms the earlier claims of an increased incidence of rheumatoid arthritis in these patients.

From the practical viewpoint it is interesting that three of these patients presented at a rheumatological clinic and were recognised as having hypogammaglobulinaemia only because of their history of recurrent chest infections. They present a valuable opportunity to study the aetiology of arthritis by careful search for micro-organisms and by evaluating treatment with plasma known to lack antibody to a possible aetiological agent such as rubella virus.

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