Primary hypogammaglobulinaemia and arthritis

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Abstract

Arthritis may be the first clinical manifestation of primary hypogammaglobulinaemia. In 16 years of 281 patients who had immunodeficiency, 30 had arthritis at presentation. It was more common in Bruton's disease (15 (22%) of 69 patients) than in other forms of immunodeficiency (15 (7%) of 212 patients). Non-septic arthritis was more prevalent than septic arthritis, particularly monoarticular arthritis in Bruton's disease and pauciarticular disease in common variable immunodeficiency. Boys in whom a diagnosis of Bruton's disease was delayed were likely to develop recurrent infections complicated by arthritis.

The measurement of serum immunoglobulin concentrations readily differentiates immunodeficiency from conditions such as Still's disease and dictates subsequent management.

Introduction

Patients who have hypogammaglobulinaemia typically present with recurrent bacterial infections of the respiratory tract.¹ Untreated patients are susceptible to otitis media, sinusitis, and pneumonia from encapsulated bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae*.^{2,4}

Most of these patients have X linked hypogammaglobulinaemia (Bruton's disease) or common variable immunodeficiency; they may also have arthritis as a presenting or complicating factor. In particular, children who have hypogammaglobulinaemia may present with a spectrum of arthritic disease, such as immune complex or vasculitic polyarthritis, echovirus syndrome, which mimics joint disease, knee hydroarthritis, and polyarthritis, some of which may be confused with juvenile chronic arthritis,⁵⁻¹¹ leading to delay in diagnosis and inappropriate treatment. A distinction among these disorders is important in view of their different management.

Concentrations of serum immunoglobulins and results of tests for antibody activity are normal in children who have juvenile chronic arthritis except for a few who have selective IgA deficiency while, by definition, they are decreased in children who have primary hypogammaglobulinaemia.¹²

Patients and methods

The regional immunology laboratory in Birmingham acts as a reference centre for the diagnosis and management of patients with primary hypogammaglobulinaemia.¹³ Since 1970, 281 patients who had primary hypogammaglobulinaemia have been referred by doctors in north England and Wales.

Primary hypogammaglobulinaemia was defined as a serum IgG concentration of less than 2.0 g/l with impaired immunoglobulin synthesis owing to a defect of unknown aetiology in the B lymphocytes or plasma cells. Patients whose hypogammaglobulinaemia was caused by drugs, loss of protein, premature birth, malignancy, or infections were excluded.

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X linked hypogammaglobulinaemia (Bruton's disease) was diagnosed according to the following criteria of the World Health Organisation¹⁴: male patient; onset of disease in infancy or early childhood; serum IgG concentration less than 2.0 g/l, with appreciably decreased IgA and IgM concentrations for age; absence of functional antibodies; normal cell mediated immunity; and pre-B cells present in bone marrow but no mature B cells in peripheral blood.

Late onset or common variable immunodeficiency comprised a heterogeneous group of disorders,^{14,15} usually characterised by combined B and T lymphocyte immaturity or lymphopenia, no clear cut pattern of inheritance, and the onset of symptoms at any age but especially in the age group 30-40 years.

Arthritis was classified as either septic or non-septic. Septic arthritis was characterised by the presence of a hot, red, tender, swollen joint whose septic origin was confirmed by aspiration of synovial fluid, cytology, and bacterial culture. Those who had non-septic arthritis, a less acute arthritic process without evidence of bacterial infection, were divided into those who had monoarticular arthritis in one joint; those who had pauciarticular arthritis in two, three, or four joints; and those in whom polyarticular arthritis affected five or more joints.

Results

Of the 281 patients, 200 were male and 81 were female. There were 69 patients who had Bruton's disease, of whom 43 had a family history of the condition and 26 did not. One hundred and sixty one patients had common variable immunodeficiency; of these, 96 were male and 65 were female. The remaining 51 patients (35 male, 16 female) included cases of skeletal dysplasia (nine patients), IgG and IgA deficiency (25), IgG subclass deficiency (two), Wiskott-Aldrich syndrome (one), severe combined immunodeficiency (eight), ataxia telangiectasia (four), and non-classifiable forms of immunodeficiency (two).

Table I shows the clinical presentations of the different diagnostic groups.

TABLE I—Clinical details of children who presented with hypogammaglobulinaemia. * Values are numbers (percentages) of children

	Bruton's disease (n=69)	Common variable immunodeficiency (n=161)	Miscellaneous (n=51)	Total (n=281)
Pneumonia	46 (67)	145 (90)	36 (71)	227 (81)
Recurrent upper respiratory tract infections	15 (22)	36 (22)	16 (31)	67 (24)
Malabsorption/diarrhoea	11 (16)	32 (20)	11 (22)	54 (19)
Urinary tract infections	2 (3)	2 (1)		4 (1)
Skin sepsis	12 (17)	27 (17)	16 (31)	55 (20)
Meningitis	12 (17)	8 (5)	3 (6)	23 (8)
Arthritis	15 (22)†	12 (7)†	3 (6)†	30 (11)

*Some patients presented with more than one organ or system affected.
† $\chi^2 = 13.4$, $p < 0.01$.

In patients who had Bruton's disease no significant differences in presenting features were found between those who had a family history of the disease and those who did not. Nor were there any significant differences between male and female patients who had common variable immunodeficiency. Cases of Bruton's disease and common variable immunodeficiency were therefore not further subdivided.

The most common presentation, irrespective of the diagnostic group, was pneumonia. Although presentation with arthritis was quite uncommon in patients who had common variable immunodeficiency and miscellaneous forms of immunodeficiency, it occurred in 15 patients (22%) who had Bruton's disease. The average age of all patients who had Bruton's disease when the condition was diagnosed was 2.2 years but was higher (3.5 years) in those who presented with arthritis.

Boys who had Bruton's disease were more likely to present with septic arthritis or monoarticular arthritis, while pauciarticular was most often

found in patients who had common variable immunodeficiency (table II). Polyarthritis was found in all groups of patients.

Once treatment with replacement immunoglobulin had been started arthritis was rather uncommon, though sporadic cases of polyarthritis unresponsive to immunoglobulin were seen in all groups of patients (table III).

TABLE II—Type of arthritis at presentation

	Bruton's disease (n=69)	Common variable immunodeficiency (n=161)	Miscellaneous (n=51)
Septic	4	2	
Non-septic:			
Monoarthritis	7		
Polyarthritis	3	4	2
Pauciartthritis	1	6	1

TABLE III—Number (percentage) of patients in whom arthritis occurred as a complication

	Bruton's disease (n=69)	Common variable immunodeficiency (n=161)	Miscellaneous (n=51)
Septic	1	1	
Non-septic:			
Monoarthritis		1	1
Polyarthritis	3	1	2
Pauciartthritis		1	
Total	4 (6)	4 (2)	3 (6)

Illustrative case histories

CASE 1

A Pakistani boy born in March 1977 suffered recurrent bouts of respiratory tract infections, otitis media, and abdominal pain from the age of 5 months. In 1980 he developed persistent arthritis with effusion in the right knee, diagnosed initially as septic arthritis, despite no bacterial culture, and subsequently as Still's disease. He was treated with anti-inflammatory agents and a single injection of steroids. Tenosynovitis of the right wrist was noted in July 1981. He had a persistent cough and sputum with recurrent secretory otitis media, requiring the insertion of grommets.

In August 1982 he was admitted to hospital with pneumonia. Later that year a synovial biopsy of the right knee showed "chronic synovitis with lymphoid aggregates and fibrin deposition, consistent with rheumatoid arthritis." In February 1983, after further pneumonia in the left lower lobe caused by *H influenzae*, his serum proteins were analysed and hypogammaglobulinaemia and antibody deficiency noted (IgG 0.2 g/l, IgA 0.09 g/l, IgM 0.38 g/l).

He had three healthy sisters, but, of his four brothers, two asymptomatic younger brothers were also found to have hypogammaglobulinaemia. His total peripheral blood lymphocyte count was normal, with over 90% T cells, but he lacked detectable B cells. After treatment with replacement immunoglobulin was started his joint symptoms improved, and he had no further admissions for pneumonia.

CASE 2

A white boy born in February 1978 developed facial boils and a lip infection at the age of 8 months. In April 1981 he presented with a swelling on the dorsum of the right foot, swelling of the left knee, and pain and restricted movement of the left elbow. The results of tests for antinuclear factor and the latex test for rheumatoid factor were negative. Treatment with non-steroidal anti-inflammatory agents was started.

In June 1981 he was admitted with septic arthritis in the right knee. *Staphylococcus aureus* was cultured, and the arthritis responded to intramuscular flucloxacillin and oral fusidic acid. The next month his serum was analysed, and hypogammaglobulinaemia and antibody deficiency were detected (IgG 0.01 g/l, IgA 0.05 g/l, IgM 0.05 g/l). After treatment with replacement immunoglobulin was started his joint symptoms settled, and he remained well.

There was no family history of recurrent infections or deaths in infancy,

but he had a brother aged 8 months who was also found to have hypogammaglobulinaemia. Neither boy had any detectable surface immunoglobulin positive B cells among his peripheral blood lymphocytes. The younger brother was initially asymptomatic, but at the age of 18 months he developed monoarthritis in his right knee. He started receiving treatment with replacement immunoglobulin, after which he also remained well.

Discussion

Of 281 patients who had primary hypogammaglobulinaemia, 22% of boys who had Bruton's disease and 7% of patients who had common variable immunodeficiency presented with non-septic arthritis. Patients who had Bruton's disease were particularly likely to present with recurrent bacterial infections of the respiratory tract and to develop arthritis. The diagnosis in boys presenting solely with arthritis is often delayed. Two cases of children who had hypogammaglobulinaemia initially misdiagnosed as juvenile chronic arthritis have been described in detail, but delays in diagnosis have been recorded in several others.

Juvenile chronic arthritis of systemic onset (Still's disease) presents classically in children under the age of 5 as a trio of fever, characteristic rash, and arthritis.^{16,17} As Bruton's disease occurs in boys of a similar age there may be a diagnostic difficulty in the early stages, but measurement of serum immunoglobulin concentrations and antibody activity readily distinguishes hypogammaglobulinaemia from these conditions.

In addition to the arthritic syndrome discussed above children deficient in antibody may present with a non-infective knee arthrosis that resembles monoarticular juvenile chronic arthritis. They are also susceptible to joint infections with mycoplasma and ureaplasma that require specialised culture facilities to isolate them from joint aspirates.¹⁸

Although non-steroidal anti-inflammatory agents are a useful adjunct in treating the active stages of arthritis in patients who have hypogammaglobulinaemia, a long term solution is likely to be achieved only after the correct diagnosis has been made and treatment with replacement immunoglobulin started.

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