Thyroid function tests in patients with cortisol deficiency before and after cortisol replacement

Case No	Age at diagnosis (years)	Sex	Treatment interval (months)	Free thyroxine index		Thyroid-stimulating hormone (mU/l)	
				Before replacement	After replacement	Before replacement	After replacement
1	48	M	72	35	76	31	1.1
2	45	F	96	24	32	61.4	1.4
3	21	M	8	77	88	28	4.8
4*	60	M	12	62	123	17.6	3.8

*Isolated adrenocorticotrophic hormone deficiency.

activity. Two cases of isolated adrenocorticotrophic hormone deficiency had been diagnosed by standard tests of the hypothalamus-pituitary-adrenal axis. All patients had tests of thyroid function performed at presentation, which were repeated at intervals after glucocorticoid treatment.

Six of the patients with Addison's disease had normal free thyroxine indices (normal range 50-160) and thyroid-stimulating hormone concentrations (normal range 0.5 mU/l) at presentation. Five patients had raised thyroid-stimulating hormone concentrations; four of these also had low free thyroxine indices and therefore received thyroxine treatment. In two of these patients the treatment was subsequently stopped; the free thyroxine index fell rapidly in one (free thyroxine index 32 at four weeks with normal concentration of thyroid-stimulating hormone; see table, case 2), who felt unwell and was treated again with thyroxine. The other patient (see table, case 1) remained euthyroid and was well without taking thyroxine 14 weeks later.

Both patients with isolated adrenocorticotrophic hormone deficiency had raised thyroid-stimulating hormone concentrations at diagnosis. One had a normal free thyroxine index and raised thyroid-stimulating hormone concentration, which became normal with cortisol replacement (case 4). The other had a low/normal free thyroxine index and raised thyroid-stimulating hormone concentration and is taking thyroxine. Details of patients with high thyroid-stimulating hormone concentrations and who were restudied without receiving thyroxine (two cases) or were restudied after thyroxine was stopped (two cases) are shown in the table.

No difference was found in the severity of cortisol deficiency in those patients with and without raised thyroid-stimulating hormone concentrations as judged by the pretreatment concentration of cortisol (at 8 00 am) (mean 270 ± 54 , range 84-580 nmol/l *v* mean 140 ± 39 , range 20-317 nmol respectively) or cortisol increment after 250 µg synacthen intramuscularly (mean 99 ± 53 , range 0-285 nmol/l *v* mean 124 ± 50 , range 0-248 nmol/l respectively).

Of the five cases of Addison's disease with raised thyroid-stimulating hormone concentrations (at diagnosis), three had positive test results for both adrenal and thyroid microsomal antibodies and two also had anti-thyroglobulin antibodies. Of six patients with normal thyroid-stimulating hormone concentrations, adrenal antibodies were found in three, but none had thyroid antibodies. The two cases with adrenocorticotrophic hormone deficiency were both autoantibody-negative.

Comment

Seven of the 13 cases with cortisol deficiency had raised concentrations of thyroid-stimulating hormone. Of these, two had normal thyroid-stimulating hormone concentrations after glucocorticoid replacement and were euthyroid two years and five months respectively after treatment. One further patient has since been taken off thyroxine and has remained euthyroid. The two patients with Addison's disease presenting with raised thyroid-stimulating hormone concentrations and who are now euthyroid both had positive test results for adrenal and thyroid antibodies. This reversion to normal values of thyroid-stimulating hormone after cortisol replacement could be due to resolution of autoimmune thyroid disease. Indeed, steroid treatment may improve thyroid function in Hashimoto's disease but only in high dosage.³ Alternatively, chronic cortisol deficiency may impair the thyroid response to thyroid-stimulating hormone or promote secretion of the hormone directly.^{2 4 5} The changes in our patients with isolated adrenocorticotrophic hormone deficiency (both of whom had no thyroid antibodies) favour this latter mechanism. Several factors may, of course, operate together, particularly in those patients with thyroid antibodies.

These cases indicate that excess thyroid-stimulating hormone is not necessarily an indicator of long-term thyroid hypofunction in untreated cases of glucocorticoid deficiency. Indeed, thyroid-stimulating hormone concentrations often returned to normal with treatment. This is well illustrated by the patient who was receiving thyroxine for six years before treatment was discontinued.

Correspondence and requests for reprints should be addressed to: Professor E A Espiner, Department of Endocrinology, Princess Margaret Hospital, Christchurch 2, New Zealand.

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Department of Endocrinology, Princess Margaret Hospital, Christchurch, New Zealand

ANTHONY H BARNETT, MD, MRCP, senior registrar

RICHARD A DONALD, PHD, FRACP, professor

ERIC A ESPINER, MD, FRACP, professor

Guillain-Barre syndrome associated with Campylobacter infection

The term "acute infective polyneuritis" supposes an infective agent as its cause, though this has rarely been confirmed. A preceding gastrointestinal illness has been noted in 10-20% of cases,¹ but again an infective agent has rarely been isolated. We report a case of Guillain-Barre syndrome which occurred after a gastrointestinal illness associated with *Campylobacter* in the stools and a raised serum antibody titre to *Campylobacter*.

Case report

A 45-year-old man was admitted as an emergency with a five-day history of diarrhoea, abdominal pain, and rectal bleeding. Five days before admission he had been taking the analgesic zomepirac sodium (Zomax) for backache. On admission he was febrile with a temperature of 37.5°C; he had familial clubbing and acute tenderness both suprapubically and anteriorly on rectal examination. A barium enema showed only a few small diverticula in the sigmoid colon. He was treated initially with oral ampicillin and metronidazole. Seven days after admission a stool culture grew *Campylobacter* and his treatment was changed to oral erythromycin. Subsequently, a serum antibody titre to *Campylobacter* was 1/600. Three days after starting erythromycin he developed weakness of his left arm and an absent left triceps jerk. This rapidly progressed to symmetrical and pronounced weakness and wasting of his arms and legs, which left him with little shoulder movement, minimal finger flexion, and the ability just to flex his legs and dorsiflex his left foot. Within three days all tendon reflexes were lost. There were no cranial nerve lesions and no abnormal sensory signs apart from hyperaesthesia of the hands and feet.

The results of investigations which proved to be normal included serum electrolyte estimations, chest radiography, cytomegalovirus and mycoplasma titres, thyroid function tests, creatinine phosphokinase, serum lead, and immunoglobulin concentrations, monospot test, and urinary porphyrin concentrations. Haemoglobin was 15.4 g/dl, white cell count $14.0 \times 10^9/l$ with an 88% neutrophilia showing a left shift. Cerebrospinal fluid obtained 13 days after the onset of polyneuritis showed no cells but a protein concentration of 650 g/l rising to 900 g/l a week later. Repeated electrophysiological studies (from 21 days after the onset of weakness) showed evidence of a mild-to-moderate segmental demyelination in the peripheral nerves both motor and sensory (lowest nerve conduction velocity 35 ms in the

median nerve) with lesions of the proximal segments (F-wave latency 62-ms on stimulating the tibial nerve at the ankle). There was a pronounced and widespread axonal degeneration, reflected in the small amplitude of the muscle and nerve potentials in nerve conduction velocity studies, and profuse fibrillations or positive sharp waves in muscles at rest on the electromyogram. These findings were compatible with a polyneuritis with severe axonal loss. Subsequent progress has been disappointingly slow, and the patient has been confined to a wheelchair for eight months since the onset.

Comment

The initial gastrointestinal illness with bloody stools suggested a *Campylobacter* infection; this was confirmed by the high antibody titre and by stool culture, which grew a *Campylobacter* species at high temperatures to identify it as one of the *C. coli/C. jejuni* group. The subsequent neurological illness was consistent with a clinical diagnosis of the Guillain-Barré syndrome.¹ Though this syndrome may follow a gastrointestinal illness² an organism is rarely isolated from the stools, though a *Salmonella* species was found in two cases.^{3,4} Sixteen cases of Guillain-Barré syndrome occurred after an outbreak of water pollution, in which 5000 people had diarrhoea but no definite causative organism was found.⁵ So far as we are aware no case has been reported after *Campylobacter* infection. In our patient the Guillain-Barré syndrome occurred two weeks after the initial infection. This interval is similar to that seen after other gastrointestinal illnesses and suggests that the Guillain-Barré syndrome was triggered by the infection. There is no report of this syndrome occurring with any of the drugs he had received. Since *Campylobacter* infections have been recognised only in recent years, and the organism may be difficult to isolate from the stools, previous cases of *Campylobacter* infection associated with the Guillain-Barré syndrome may have been missed. Serum antibody titres to *Campylobacter* may help to resolve this in future cases of the Guillain-Barré syndrome associated with a gastrointestinal illness.

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Western Hospital, Southampton SO9 4WQ

K M RHODES, MB, MRCP, medical registrar
A E TATTERSFIELD, MD, FRCP, reader in medicine

Acquired inhibitor to human factor VIII associated with paraproteinaemia and subsequent development of chronic lymphatic leukaemia

Apparently benign paraproteinaemia is relatively common in the elderly, with a 3% incidence in those over 70 and 12% in those over 80.¹ It is sometimes associated with subsequent development of B-cell lymphoid neoplasm. Acquired inhibitors to factor VIII associated with paraproteinaemia have also been noted in otherwise healthy people (often elderly), in autoimmune diseases, particularly systemic lupus erythematosus, post partum, and in various malignancies.²

We describe a case in which a factor VIII inhibitor appeared five years after a paraprotein was noted and in which chronic lymphatic leukaemia developed eight years later.

Case report

A 66-year-old woman presented with bronchial asthma which was eventually controlled with prednisolone 5 mg daily. Incidental findings were a raised erythrocyte sedimentation rate and an IgM paraprotein band. Total IgM

was only moderately raised, IgA and IgG values were normal, and no urinary Bence Jones protein was present. Blood count showed 14% eosinophils but was otherwise normal.

Five years later the patient presented with haematuria followed three weeks later by extensive soft-tissue haemorrhage in both arms after minor trauma. Investigations showed partial thromboplastin time 99 s (control 52 s) and whole-blood clotting time 37 min (normal 4-9 min). Prothrombin time, bleeding time, thrombin time, platelet count, and fibrin degradation products were normal. Full blood count showed a normochromic normocytic anaemia, haemoglobin concentration 10 g/dl, white cell count $15 \times 10^9/l$ (98% neutrophils, 2% lymphocytes), and a normal platelet count. Factor VIII was undetectable and high-titre inhibitor to factor VIII was present. Antinuclear factor titre was positive at 1/100, C₄ concentration was reduced, LE cells were not detected, and all immunoglobulin values had fallen compared with before (IgM 2.9 g/l, IgA 0.6 g/l, IgG 4.2 g/l). (DNA binding was not tested initially but was subsequently found to be normal.)

Prednisolone 30 mg daily produced no improvement. Cyclophosphamide was added but discontinued after two months as bruising and bleeding persisted. Between 1973 and 1978 prednisolone 2.5 mg daily was continued for her asthma. Her course was punctuated by recurrent haemarthroses, haematomas, epistaxes, and on one occasion by life-threatening retropharyngeal bleeding, which responded to intensive plasmapheresis and cryoprecipitate treatment.

In 1979 herpes zoster developed, followed by widespread varicella. The blood count was normal, haemoglobin concentration 13.0 g/dl, white cell count $7.4 \times 10^9/l$ (76% neutrophils, 16% lymphocytes, 8% monocytes), and platelet count $270 \times 10^9/l$. Analysis of the surface membrane showed a normal total lymphocyte count with normal proportions of T and B lymphocytes and no evidence of monoclonal expansion, but there was gross impairment of lymphocyte transformation in response to pokeweed mitogen and phytohaemagglutinin. The lymphocyte count rose exponentially from 1980 and results of surface-marker analysis in 1981 were typical of chronic lymphatic leukaemia,³ showing monoclonal expansion of B cells bearing IgM and IgD surface immunoglobulins with lambda light chains and rosette formation with mouse erythrocytes. The total IgM concentration had fallen to 2.0 g/l, the IgA value remained low at 0.25 g/l, and IgG was normal at 7.85 g/l. There had been no bleeding episodes since August 1980, the partial thromboplastin time was normal, and no factor VIII inhibitor was detectable. At no time was lymphadenopathy, splenomegaly, or other clinical features of chronic lymphatic leukaemia present. The chart shows the changes in lymphocyte count, IgM concentration, and partial thromboplastin time during 1969 to 1982.

Changes in lymphocyte count (●—●), IgM concentration (●---●), and partial thromboplastin time (○—○) during 1969-82.

Comment

Acquired factor VIII inhibitor has been reported in association with non-Hodgkin's lymphoma⁴ and myeloma⁵ but not with chronic lymphatic leukaemia. In our patient the temporal sequence was reversed; overt chronic lymphatic leukaemia occurred many years after the presenting illness and its appearance seemed to parallel an improvement in her coagulopathy.

The relation between the various immune phenomena are intriguing and the question remains whether the monoclonal IgM, presence of autoantibodies, and impaired lymphocyte transformation represented early signs of occult chronic lymphatic leukaemia or whether their presence in some way predisposed to the eventual emergence of a clone of malignant lymphocytes. This case demonstrates well the prolonged time course and variability of B-cell malignancy and its associated phenomena.

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