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Insulin resistant diabetes mellitus associated with acanthosis nigricans and systemic lupus erythematosus in a Nigerian male

A. F. BELLA, T. A. AKINTEWE AND O. O. FAMUYIWA
Department of Medicine, University College Hospital, Ibadan, Oyo State, Nigeria

Summary

A case is reported of diabetes mellitus associated with insulin resistance, acanthosis nigricans and systemic lupus erythematosus. This will be the first such case described in a Nigerian and most likely the first case in an African, of this recently characterized syndrome. An awareness about this syndrome by physicians in this environment should lead to a prompt referral to where there are adequate facilities for an early diagnosis which could prove to be life-saving.

Résumé

Un cas de diabète résistant à l'insuline associé à l'acanthosis nigricans et au lupus érythémateux disséminé, a été rapporté. Ce syndrome récemment caractérisé est le premier cas décrit chez un Nigérien. Une meilleure conscience de ce syndrome par les médecins dans cet environnement devrait permettre de diriger le patient vers un service adéquat pour un diagnostic précose qui pourrait être salvateur.

Introduction

Although there have been earlier reports on the association between diabetes mellitus, insulin resistance and acanthosis nigricans (Winkleman, Scheen & Underdahl, 1960; Field, Johnson & Harring, 1961; Tucker, Klink, Goetz *et al.*, 1964), the full spectrum of the syndrome and the nature of the insulin-receptor abnormality was described by Flier *et al.*, (1975; 1976) and Kahn *et al.* (1976). They divided the syndrome into two groups. Type A patients are usually young females who in addition to the glucose intolerance, acanthosis nigricans and insulin resistance, also show signs of virilization or accelerated growth (Kahn *et al.*, 1976). The insulin receptor abnormality is primary; the decreased insulin binding being due to a decrease in the number of receptors (Bar *et al.*, 1980). Type B syndrome on the other hand occurs in older females who characteristically show evidence of autoimmune disease. These patients have circulating antibodies directed against the insulin receptors which cause decreased insulin binding due to a decrease in receptor affinity (Bar *et al.*, 1980).

The clinical course of this syndrome has been described in detail (Flier *et al.*, 1978). Although all the first reported cases were in females, a few cases have recently been reported in males (Omori *et al.*, 1982). Variants of the syndrome have also been described which may not show dermatologic features (Baldwin *et al.*, 1979). We describe here a type B syndrome in a young Nigerian male which is also noteworthy because of its association with systemic lupus erythematosus (SLE), a disease encountered very uncommonly in Nigerians.

Correspondence Dr. O. O. Famuyiwa, Department of Medicine, University College Hospital, Ibadan, Oyo State, Nigeria.

Clinical case history

The patient was a 19-year-old male student who was diagnosed as an insulin-dependent diabetic in April 1980. He was admitted to the University College Hospital (UCH), Ibadan and stabilized on 20 units soluble insulin and 60 units insulin zinc suspension (IZS Lente) daily. In July 1980, he was admitted with a diagnosis of

pyrexia of undetermined cause and although blood cultures were negative for *Salmonella typhi*, he responded well to treatment with Chloromycetin (Chloramphenicol).

In April 1981, he was noticed to be losing weight, having lost 5 kg within 3 months despite good control of his diabetes. About the same time, he complained of intermittent fever and arthralgia involving the knees and elbows. It was in November 1981 that he was readmitted into the hospital for investigation of the persistent weight loss. While on the ward, he developed cough, dyspnea and pleuritic chest pain. He had tachycardia and pleural rub but no other signs in the chest. His chest X-ray showed bilateral basal fluffy infiltrates and a presumptive diagnosis of atypical or mycoplasma pneumonia was made; confirmatory serodiagnostic tests were not readily available. Although his temperature settled on treatment with Ampiclox and Gentamycin, his overall clinical condition remained poor. At this time he was noticed to have bilateral axillary acanthosis nigricans. His diabetes became difficult to control; in spite of over 200 units of insulin daily in divided doses, he had persistent 2% glycosuria and his blood sugar ranged between 300 and 400 mg%. On the suspicion that circulating insulin antibodies to beef-pork insulin preparation might be contributing to the insulin resistance, he was placed on monocomponent pure pork insulin. Following this change in insulin preparation, a much lower dose of 15 units Actrapid (short acting) and 45 units Monotard (intermediate acting) was required to control his diabetes.

In February 1982, he developed lymphadenopathy involving the posterior triangles of the neck and both axillae. He also had pains over both feet and the tips of the toes. There was clinical evidence of neuropathy characterized by profound weakness and wasting of muscles of all four limbs and a right lateral peroneal nerve palsy. He later developed peri-orbital edema, conjunctivitis and chemosis of both eyes and bilateral parotid gland enlargement. Because of his worsening clinical condition and the limited laboratory resources available to do a more comprehensive investigation that would delineate his multiple clinical problems, he was referred to a clinic in London, England for further evaluation.

Laboratory data

The following are the results of some of the investigations done during the patient's hospitalization in London. The erythrocyte sedimentation rate (ESR) was 131 mm/h, the haemoglobin 8.9 g/dl and the white cell count with differentials was reported as normal. The platelet count was 127×10^9 and the reticulocyte count 5.5%. Liver function tests revealed raised SGOT 77 units; globulins 8.3 g/dl and decreased albumin 2.2 g/dl; Na^+ 132 Eq/l; K^+ 4.3m Eq/l; Cl^- 144m Eq/l; HCO_3 13m Eq/l; urea 37 mg/dl and creatinine clearance 53 ml/mm. Serum immunoglobulins were elevated; IgG 50.6 g/l, IgA 5.3 g/l and IgM 4.4 g/l. Protein electrophoresis showed massive polyclonal increase in γ-globulin and some increase in α_2 globulin. Chest X-ray showed patchy shadowing at the bases. Histology of a lymph node biopsy showed marked reactive follicular hyperplasia associated with vascular proliferation and infiltration of the inter-follicular pulp with plasma cells and a few immunoblasts. There were extensive areas of necrosis resulting in much nuclear debris and macrophage response. The picture was felt to be consistent with SLE. Bone marrow showed megaloblastic hemopoiesis. Anti-nuclear factor was strongly positive (ring pattern) in 1:10,000 titer and anti-smooth muscle antibody was also positive. Antibodies against thyroglobulin, thyroid microsomes, gastric parietal cells and mitochondria were negative. Blood, urine, sputum and stool cultures showed no growth. Twenty-four hour urinary protein was initially 2.4 g but it increased terminally to 18.3 g. Cerebrospinal fluid protein was 218 mg/dl and culture showed no growth. The ECG showed sinus tachycardia.

Anti-receptor antibody–anti-receptor antibody was present in a titer of 1:50 but anti-insulin antibodies were not detected (assays done by Dr Simeon Taylor, National Institutes of Health, Bethesda, Maryland, USA).

Hospital course (in London)

The patient remained very ill at the London clinic with persistent fever, tachycardia and respiratory distress. He was treated with intravenous Tobramycin and Cephamandol without any improvement in the chest lesions.

Because of the strong suspicion of SLE, he was started on large doses parenteral prednisolone. There was an initial dramatic response as his fever settled down, but this was short-lived and other problems soon emerged. Significantly, while on steroid therapy, his daily insulin requirement became extremely variable. He had episodes of hypoglycemia even when insulin was not administered. He progressively became worse and he died 19 days after admission. An autopsy was not performed.

Discussion

Following the initial reports of Flier *et al.*, (1975), the syndrome of insulin-resistant diabetes mellitus with or without acanthosis has been reported from other parts of the world (Kibata *et al.*, 1975; Omori *et al.*, 1982). The heterogeneity of the syndrome has been increasingly recognized and it is now known that patients who have anti-insulin or anti-receptor antibodies may present with hypoglycemia instead of hyperglycemia because the antibodies are of a receptor-stimulating type (as in Graves' disease) instead of a receptor-blocking type (Anderson *et al.*, 1977; Goldman *et al.*, 1979; Taylor *et al.*, 1982). The syndrome must also be distinguished from other causes of extreme insulin resistance such as leprechaunism (Taylor *et al.*, 1982). Flier *et al.* (1978) in their follow-up of patients with type B syndrome showed that the clinical course is extremely variable, often fluctuating between an insulin-resistant state and an insulin-sensitive state. This is probably due to spontaneous changes in antibody titer and/or independent changes in receptor concentration.

There is enough evidence to justify that this patient had features of type B syndrome. He had diabetes mellitus and acanthosis nigricans. He demonstrated insulin resistance in the course of his illness when he required more than 200 units of insulin daily and with blood sugar values between 300 and 400 mg%. Significantly, his serum was positive for anti-receptor antibodies and these must have been of pathogenetic significance. There were clear-cut clinical and laboratory features of an autoimmune disease as evidenced by the long-standing history of fever, arthralgia and weight loss despite good control of diabetes; high sedimentation rate, raised polyclonal γ-globulins and diffuse infiltrates in the lungs did not respond to antibiotics and gross proteinuria. This was confirmed to be SLE by the positive anti-nuclear factor and positive anti-smooth muscle antibody. On treatment with glucocorticoids, there was an initial clinical improvement but more importantly, the patient developed hypoglycemic episodes. This would be an unusual development in most diabetics if treated with glucocorticoids when the diabetes would be expected to worsen. Flier *et al.* (1978) have reported a progressive fall in anti-receptor antibody titer in a patient with type B syndrome during treatment with corticosteroids. Coincident with the fall in titer, insulin receptor binding was observed to become normal. A similar sequence of events could explain why our patient developed hypoglycemic attacks after treatment with steroids. It is also possible that the prednisolone may have acted directly to block anti-receptor antibodies as was recently suggested by Taylor *et al.* (1982) in their report of a case of hypoglycemia associated with anti-receptor antibodies.

This is most likely the first reported case of this syndrome in an African. A computer search of the world literature in all languages did not uncover a single reported case in an African. It is noteworthy because of its association with SLE, a disease which is seen very rarely in Nigerians. The case has been reported so that an awareness of the syndrome by primary physicians could lead to a prompt referral to a tertiary care facility where an early confirmatory diagnosis can be made and proper treatment initiated.

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