Antibodies to Tubulin and Microtubule-Associated Proteins

A Study in Diabetes Mellitus, Systemic Lupus Erythematosus, and Rheumatoid Arthritis

N. A. CULLUM,*1 J. W. COLEMAN,2 I. F. CASSON,3 AND W. G. McLEAN2

Departments of Nursing and Pharmacology and Therapeutics, University of Liverpool; and Royal Liverpool Hospital, Liverpool, UK

Received February 5, 1991; Accepted June 4, 1991

ABSTRACT

We report the results of a study of serum antibodies to proteins of the nerve cytoskeleton in patients with Type I and Type II diabetes mellitus, both with and without clinical signs of diabetic neuropathy. In contrast to previous reports, elevated levels of antibody to tubulin or glycated tubulin were not associated with either diabetes or diabetes with related neuropathy. Similarly, clinical evidence of neuropathy in patients with diabetes did not relate to increased levels of antibody to native or glycated microtubule-associated proteins (MAPs). The levels of antibody to MAPs and glycated MAPs were higher in control subjects over the age of 45 years compared with younger control subjects. Increased levels of antibody to tubulin and glycated tubulin were found in the sera of patients with systemic lupus erythematosus, but not rheumatoid arthritis.

Index Entries: Microtubules; tubulin; microtubule-associated proteins; diabetes; SLE; rheumatoid arthritis; diabetic complications; neuropathies; neuronal antibodies; autoantibodies; glycation.

*Author to whom all correspondence and reprint requests should be addressed.
INTRODUCTION

Since the advent of insulin treatment over 60 years ago, the prognosis of a patient diagnosed as suffering from diabetes is far more favorable. However, secondary complications arising from the diabetic state continue to present a major threat to both the quality and duration of life of the diabetic patient. Neuropathy is probably the most common secondary complication of diabetes, and yet its pathogenesis remains uncertain.

Autoantibodies to components of the nervous system have been implicated in a number of pathological conditions (O'Shannessy et al., 1986; Ernerudh et al., 1986; Van Doorn et al., 1987). Immunoglobulins can be internalized by neurones in the periphery and conveyed along the axon by axonal transport (Fabian and Petroff, 1987). Autoantibodies specific for neuronal tubulin, the subunit protein of axonal microtubules, inhibit intraaxonal transport of proteins (Johnston et al., 1986) and have been reported to be present in increased amounts in certain disease states, such as infectious mononucleosis (Mead et al., 1980), autoimmune thyroid disorders (Rousset et al., 1984), and parasitic infections (Howard et al., 1987).

Various workers have measured the levels of antitubulin antibodies in diabetes with different results. Rousset and coworkers (1984) found elevated levels of antitubulin antibodies in recent onset Type I diabetes, whereas others used an undefined, heterogeneous group of diabetics as a positive control group in a study of antitubulin antibodies (Howard et al., 1987).

We have extended the study of antibodies to tubulin in diabetes to include the measurement of antibodies to nonenzymically glycated tubulin and to both native and glycated microtubule-associated proteins (MAPs) in both Type I and Type II diabetic patients with and without diabetic neuropathy. MAPs copurify with tubulin and are thought to be regulators of microtubule function in vivo (for review, see Olmsted, 1986).

A group of patients with systemic lupus erythematosus (SLE) was also included as SLE is associated both with the presence of a diverse range of autoantibodies, and neuropathological defects. Rheumatoid arthritis patients were included as a positive control group as it has previously been shown (Howard et al., 1987) that increased levels of antitubulin antibody are associated with this disease.

MATERIALS AND METHODS

Selection of Patients

Ten milliliters of blood samples were collected from the following groups of patients attending local diabetic clinics: