NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS AND THE SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE: A CASE REPORT WITH VERY LATE ONSET SYSTEMIC LUPUS ERYTHEMATOSUS

S. M. MIRSATTARI,* C. POWER,† A. FINE,‡ G. S. McGINN,¶ S. LUDWICK§ and J. M. G. CANVIN§

Sections of *Neurology, †Nephrology, ‡Endocrinology and §Rheumatology, Departments of Internal Medicine, †Radiology and ¶Medical Microbiology, University of Manitoba Health Sciences Centre, Winnipeg, Manitoba, Canada

SUMMARY

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been reported in a variety of diseases of the central nervous system (CNS) [1]. However, SIADH has rarely been reported in patients with systemic lupus erythematosus (SLE) [2–7]. We report a case in which SIADH was associated with the new onset of neuropsychiatric SLE (NP-SLE) and whose course paralleled that of the NP-SLE.

CASE REPORT

A previously healthy 88-yr-old Caucasian woman presented to a tertiary care institution in October 1995 with a 6 month history of malaise, generalized weakness, arthralgias, myalgias, anorexia, weight loss, insomnia and gradual mental withdrawal. She developed a transient erythematous malar rash at the onset of her symptoms. She was on no medications and had no previous or family history of neurological, psychiatric or connective tissue diseases. On examination, she had symmetrical sensory impairment to pain and touch in a stocking distribution, decreased vibration sense and proprioception in the distal lower extremities, and absent ankle reflexes. The remainder of the examination was unremarkable. Blood pressure and heart rate were 140/70 and 72, respectively, and did not change with posture. The Folstein’s mini-mental status examination was normal (28/30). She was investigated extensively, which was remarkable only for the results discussed here. Biochemistry showed a serum sodium of 125 mmol/l with hypo-osmolar serum (256 mOsm/kg H2O). Urine sodium and osmolality were high at 48 mmol/l and 272 mOsm/kg, respectively. Uric acid was low normal at 135 μmol/l (120–360 μmol/l, normal urate) and a 24 h urine showed mild proteinuria at 0.420 g/day. A diagnosis of SIADH was made, based on a persistently low serum sodium and osmolality associated with excessive excretion of sodium in urine and a higher urine osmolality than expected in this situation. She had a significant lymphopenia (0.4 × 10⁹/l), moderately elevated ESR, and diffuse brain atrophy with extensive areas of increased signal intensity in the white matter on a T2-weighted MRI (Fig. 1). Cerebrospinal fluid studies and an electroencephalogram were unremarkable. Nerve conduction studies revealed mild–moderate sensorimotor peripheral neuropathy. Connective tissue disease screen revealed positive ANA (titre 1:160), anti-double-stranded DNA (anti-dsDNA) (67 IU/ml, normal 0–30) and antibody to antiribosomal P protein (titre 1:64). Serum complement levels were low with C3 0.38 g/l (normal 0.88–2.01) and C4 < 0.10 g/l (0.16–0.47). Extractable nuclear antigens were not present. Cardiolipin antibodies and rheumatoid factor were not present. VDRL was negative and lupus anticoagulant was not detected. This patient met 11 of the American College of Rheumatology major diagnostic criteria for SLE [8]. The course of SLE and SIADH were closely monitored for 60 weeks (Fig. 2). Attempts at fluid restriction were unsuccessful and at the third week demeclocycline was added. Four weeks later, she experienced further deterioration of her mood and was diagnosed with a major depression with psychotic features. The psychotic condition deteriorated and did not start to improve until high-dose i.v. and oral corticosteroids were introduced. A repeat titre of antiribosomal P protein antibodies at this time showed a 5-fold increase (1:320) which was associated with further decline in serum sodium to 125 mmol/l. In week 20, azathioprine was added while prednisone was gradually decreased. There was a gradual improvement in the severity of psychosis when high-dose steroids were used, but complete resolution was not seen until she had been taking azathioprine for 10 weeks. Clinical improvement was accompanied by declining serological markers of lupus activity, resolved proteinuria and improved lymphopenia to 1.3 × 10⁹/l. Over the subsequent 30 weeks, the patient remained well with marked improvement of mood and no clinical evidence of peripheral neuropathy. However, mild hyponatraemia persisted with serum sodium as low as 129 mmol/l. Only by week 60 did the SIADH resolve, with the serum sodium normalizing at 138 mmol/l and uric acid increasing to 178 μmol/l. The serological markers of the SLE disease activity also improved and have remained stable on treatment.

Serum antidiuretic hormone (ADH), aldosterone (Ald) and plasma renin activity (PRA) were measured in week 30 when the serum osmolality was 275 mOsm/kg H2O. ADH was elevated at 2.3 pg/ml (normal < 1.5) [1] but Ald and PRA were normal at 607 pmol/l (110–780) and 0.93 pmol/ml/h (0.40–2.30).

© 1998 British Society for Rheumatology
Fig. 1.—Axial, T2-weighted MRI of the brain in an 88-yr-old patient with new onset of neuropsychiatric SLE.

Fig. 2.—Evolution of SIADH, serological markers of SLE disease activity and response to therapy in an 88-yr-old patient with new onset of neuropsychiatric SLE.
DISCUSSION

This case illustrates some novel and important neurological features of SLE. Review of the literature indicates that this is the oldest reported case of neonatal SLE, which may explain the extent of neurological involvement [9]. In addition, the course of NP-SLE was closely correlated with anti-dsDNA and serum complement levels accompanied by a good response to therapy for SLE. NP-SLE and peripheral neuropathy presented very early in the disease course, and were associated with the antiribosomal P protein antibody, a type of antineuronal antibody. The antiribosomal P antibody level was increased to five times its initial level when the psychosis worsened. These antibodies have been implicated in the pathogenesis of psychosis and depression in patients with diffuse manifestations of NP-SLE, but were absent in SLE patients with steroid-induced psychosis [10]. An increase in their titre has been correlated with exacerbation of psychosis [11]. Taken together, the above findings emphasize the close relationship between SLE disease activity and the risk of NP-SLE.

The diagnosis of SIADH in our case was confirmed by clinical euolaemia in the presence of hyponatraemia with a urine osmolality and sodium that were inappropriately high [12]. Investigations ruled out other causes of hyponatraemia. Normal renal, thyroid and adrenal function with relative hypouricaemia were supportive evidence of SIADH. Extensive investigations ruled out neoplastic, pulmonary, cardiovascular and any other known causes of SIADH [1]. Thus, CNS involvement by SLE was the likeliest cause of the SIADH. Our patient also demonstrates the chronic nature of excessive ADH release, and the need for monitoring electrolytes and fluid intake of patients with NP-SLE.

SIADH is a rare manifestation of SLE with only six separate case reports previously described [2–7]. In three cases [2, 3, 4], the association between SIADH and SLE was confounded with other variables such as subarachnoid haemorrhage [2], phenobarbital use [2], pulmonary tuberculosis [2], membranoproliferative glomerulonephritis with significant proteinuria (2.5 g/day) [3] and possible infection with HIV [4] making the association between SLE and SIADH uncertain. However, the postmortem examination in one case [2] demonstrated extensive neuronal loss and gliosis in the supraoptic and paraventricular nuclei of the hypothalamus. In two cases [5, 6], there was a close association between SLE disease activity and SIADH. Trachtman et al. [13] found that clinically stable SLE patients had elevated serum ADH levels which they assumed to be secondary to antineuronal antibodies. This was confirmed in our patient with an elevated serum ADH level when hyponatraemia and SLE disease activity were improving. We speculate that antiribosomal P protein antibodies are a putative stimulator of the paraventricular and supraoptic neuronal populations of the hypothalamus resulting in excessive ADH release.

This case illustrates that SLE can present at any age, NP-SLE can cause SIADH which responds to SLE therapy. SIADH-induced hyponatraemia may be another measure of SLE disease activity and may be an early manifestation of NP-SLE. Future studies defining the neuronal subpopulations targeted by antiribosomal P protein antibodies may provide insight into exact mechanisms of NP-SLE and SIADH pathogenesis.

REFERENCES