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Addison's Disease, Psychosis, and the Syndrome of Inappropriate Secretion of Antidiuretic Hormone

E. G. LEVER and S. A. STANSFELD

Summary: A case of tuberculous Addison's disease presenting with psychosis, profound hyponatraemia, and detectable plasma antidiuretic hormone is reported. Clinical and biochemical improvement after corticosteroid replacement was followed by relapse with further psychosis and inappropriate antidiuretic hormone secretion: both were promptly reversed by demethylchlortetracycline. The association of psychological symptoms with Addison's disease, the role of anti-diuretic hormone secretion in Addison's disease, and the inter-relationship between Addison's disease, psychosis and anti-diuretic hormone secretion are discussed.

Addison's original description of the disease drew attention to the psychological symptoms of anxiety, insomnia and confusion. Psychotic symptoms in Addison's disease are uncommon, occurring usually with mood change and delirium (McFarland, 1963). Various metabolic mechanisms have been proposed although none conclusively demonstrated. Prior to corticosteroid replacement psychosis may be related to sodium and potassium ion flux (Michael and Gibbens, 1963), or more rarely, to hypoglycemia (Cohen and Marks, 1961). After treatment psychosis may be attributed to excessive corticosteroid replacement, or possibly to steroid hypersensitivity in a corticosteroid-deprived brain. Psychosis in Addison's disease has not previously been described in relation to disturbances of antidiuretic hormone (ADH) secretion although cyclical water retention in some periodic psychotic patients may be partly produced by ADH (Goodwin, J. C. and Jenner, F. A.).

A case is described in which psychosis occurred in the presentation of the disease, during the initial course of corticosteroid replacement, and as a late manifestation several months after initiation of treatment. An attempt to associate corticosteroid status, mental symptoms and plasma ADH levels is made. It is proposed that the sub-acute organic reaction was due to water intoxication resulting from persistent ADH secretion.

Case report

P.W. is a married man with three children. He began work at 16 years as an apprentice carpenter and was invalided out of the Army at 24 years when he was treated for spinal tuberculosis with drugs and arthrodesis. He then continued in employment in two less physically demanding jobs until he retired from his job as a messenger at the age of 50 years because of increasing fatigue. He is the youngest of six siblings. He has no previous history of psychiatric disorder and there is no family history of mental illness.

At 53, over a period of 4 weeks, he became withdrawn and developed ideas of reference that there was a variety programme on the television aimed directly at him alone. He also developed delusions concerning the penetration of his house by electronic beams, and auditory hallucinations. These symptoms diminished on treatment with trifluoperazine and orphenadrine which were discontinued because of his worsening physical condition. Three months prior to his admission to hospital, he lost his appetite, libido and 12 kilograms in weight. He became lethargic and ataxic, with difficulty initiating voluntary movements (not reversed by orphenadrine).

On admission five months after his first psychiatric symptoms he was thin but not dehydrated or pigmented. His blood pressure was 115/70 mm Hg supine, 90/50 mm Hg erect. He had a dorsal gibbus, generalised muscular hypertonus, and an impassive facies.

He was mildly depressed in mood and pre-occupied with delusions and second person auditory hallucinations. He demonstrated well-systematised delusions involving the post office who, he believed, were passing laser beams through his house and through his radio and T.V. He did not exhibit thought withdrawal, thought insertion, or thought broadcasting. He was alert and orientated and showed no abnormalities on detailed cognitive testing apart from minor difficulties

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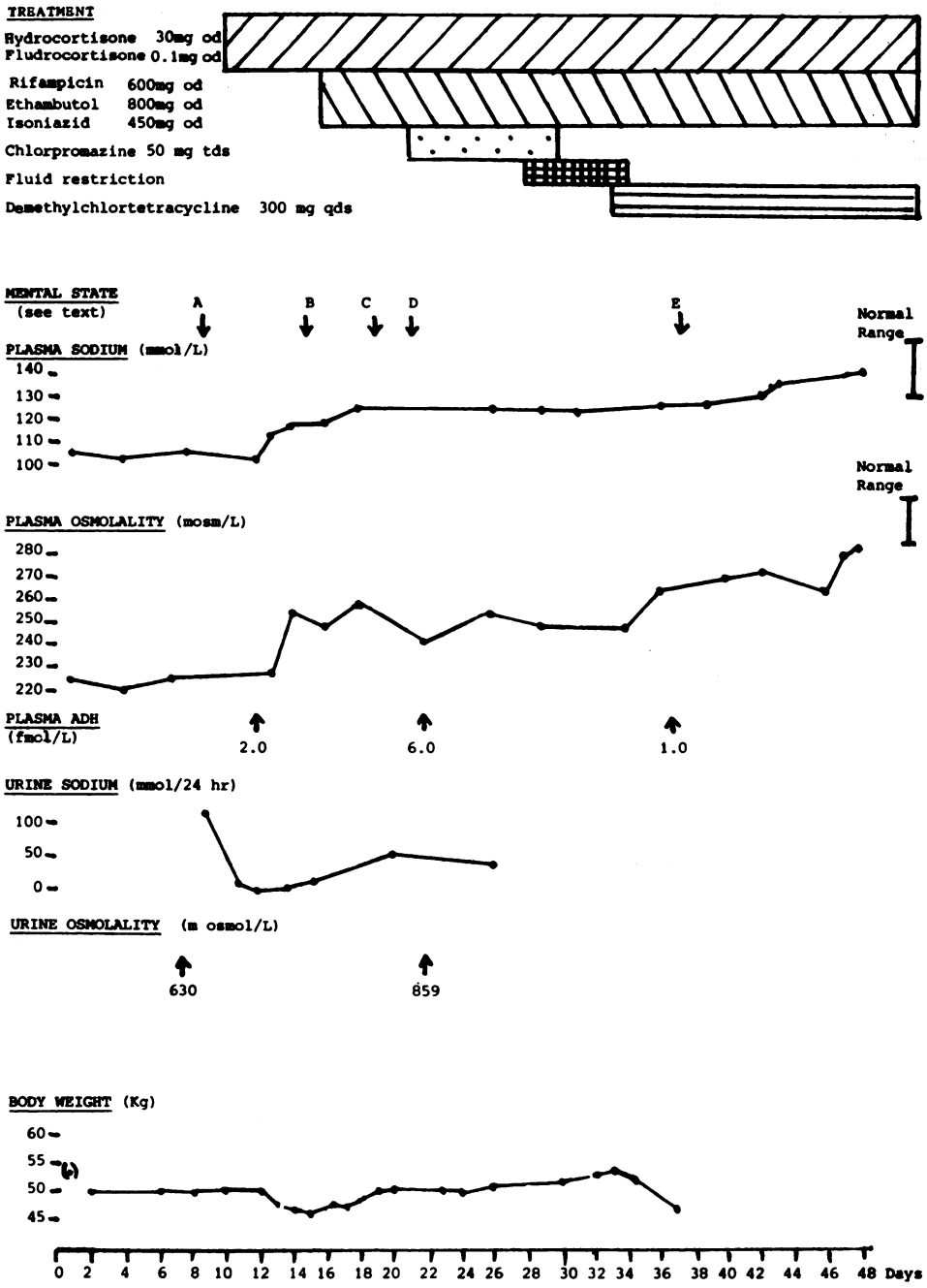

FIG 1

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with new learning. (Fig 1, A). (The mental states described in the text are denoted on Fig 1 by letters A–E).

Initial investigations (normal ranges in brackets) showed plasma sodium 99 mmol/L (130–145 mmol/L), potassium 5.9 mmol/L (3.5–5.0 mmol/L), urea 4.7 mmol/L (3.3–6.7 mmol/L), glucose 5.7 mmol/L (2.8–5.0 mmol/L), plasma osmolality 220 mosm/L (280–295 mosm/L), and urine osmolality of 630 mosm/L. Hormone assays showed low normal 9 a.m. cortisol of 220 nmol/L (280–710 nmol/L) with an ACTH level of 260 mU/L (<80 mU/L), elevated plasma renin 12.3 pmol/hr/ml (1.17–2.39 pmol/hr/ml recumbent), and a low plasma aldosterone 40 pmol/L (100–500 pmol/L recumbent). Plasma ADH by radioimmunoassay was 2 fmol/L (0.9–3.8 fmol/L). This was inappropriately elevated in relation to the low plasma osmolality. Sixty minute and 3-day 'synacthen' tests failed to stimulate plasma cortisol. Adrenal antibodies were negative. Radiographs showed pleural and adrenal calcification and a lower dorsal gibbus. C.T. head scan and EEG were normal. The subsequent course of treatment, and levels of plasma sodium, plasma osmolality, plasma A.D.H., urinary sodium excretion and osmolality, and body weight are shown in Fig 1.

The patient was started on hydrocortisone 30 mg daily fludrocortisone 0.1 mg daily, and triple therapy comprising rifampicin, isoniazid and ethambutol, but no neuroleptic drug. Five days later his delusions disappeared, his face became expressive, and muscle tone returned to normal, with rapid initiation of voluntary movements. (Fig 1, B).

Plasma sodium rose to 116 mmol/L and urinary sodium excretion fell from 114 to 1 mmol/L. Plasma osmolality remained low and his weight fell from 50 to 47 kg. Four days later he became hypokinetic, with recurrence of delusions, ideas of reference, and impairment of short-term memory. (Fig 1, C). After a further two days he was euphoric and disinhibited with fluctuating disorientation in time and place, suggestive of a sub-acute confusional state. (Fig 1, D). Plasma sodium was now 124 mmol/L but plasma osmolality was 242 mosm/L with urine osmolality 859 mosm/L, suggesting inappropriate antidiuretic hormone secretion (SIADH) and confirmed by ADH assay 6 fmol/L. During this time his body weight had increased from 47 to 51 kg. No fall in body weight, and no increase in plasma sodium was observed with fluid restriction (intake restricted to 500 mls plus urine output over the previous 24 hours). Low dose chlorpromazine, 50 mg thrice daily for 10 days produced only a marginal improvement. He improved rapidly after four days treatment with demethylchlortetracycline, 300 mg four times daily (Fig 1, E). His mental state returned to normal, with a rise in plasma sodium to 136 mmol/L and plasma osmolality to 280 mosm/L and a reduction in body weight of 4 kg. It is to be noted that this loss of weight, presumably the result of diuresis, occurred well before his plasma sodium returned to normal.

He relapsed into psychosis 15 weeks later in association with an elevated ADH level (9.1 fmol/L). At that time he was mildly euphoric and irritable. He had pressure of speech and language disorder which bordered on incoherence. He had both auditory hallucinations of male and female voices and delusions of a machine affecting his mind. He showed neither thought withdrawal, thought insertion nor thought broadcasting and denied passivity feelings. He was fully orientated in time, place and person and showed no impairment of memory. His symptoms responded to trifluoperazine 5 mg twice daily. Over two years' follow-up he has relapsed once after stopping trifluoperazine, displaying similar symptoms to his first relapse, and responding within 24 hours of its reintroduction. Over six months he fully regained his 12 kilogram weight loss and has maintained this weight for the last three years.

Discussion

Psychological symptoms are found in almost all patients with *severe* Addison's disease. Cleghorn (1951) found psychological changes in 92 per cent of his series of 25 patients. These comprised apathy and negativism (84 per cent), and seclusiveness, depression, and irritability (50 per cent). Stoll (1953) noted frank psychiatric abnormalities in 96 per cent of 29 patients: 50 per cent were euphoric, 25 per cent were depressed, and 25 per cent were apathetic. Indifference, diminished initiative and mood fluctuations were very common. In most of these cases there was a mild to moderate organic reaction with memory defect as the main symptom. Collected case reports of psychosis in Addison's disease (McFarland, 1967) include 10 schizophrenic, 6 paranoid, 6 affective, 2 acute undifferentiated, 1 catatonic and 1 organic psychosis. The *type* of psychosis is probably based as much on the patient's personality and life circumstances (Mattson, McFarland) as on the underlying metabolic disturbance. This case presented with a schizophrenic picture accompanied by apathy and minor memory defect. His previous personality appears to have been normal and he is happily married although he had become somewhat reclusive since his retirement.

Inability to excrete a water load is one of the characteristic metabolic abnormalities in Addison's disease. The mechanism responsible for impaired water excretion is imperfectly known. It was previously thought that glucocorticoid deficiency im-

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paired renal excretion of water directly by increasing the permeability of nephrons to water (Kleeman, 1964). Direct evidence for this using isolated perfused renal papillae is lacking (Rayson, 1978). Water-loading experiments in pure glucocorticoid-deficient rats demonstrated that plasma ADH, measured by sensitive and specific radioimmunoassay, was not suppressed, indicating that impaired water excretion in hypoadrenalism is at least partially ADH-dependent (Linas, 1980; Mandell *et al,* 1980). Reports of ADH levels in Addison's disease measured by bioassay have been variable (Kleeman, 1964; Ahmed, 1967). There have been no previous reports of radioimmunoassayable ADH levels. This case supports the animal evidence for elevation of ADH in hypoadrenalism.

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is established by the following criteria: hyponatraemia and hypo-osmolality; continued renal excretion of sodium; absence of clinical evidence of fluid volume depletion; urine less than maximally dilute in the presence of plasma hypotonicity; normal renal and adrenal function; and plasma ADH levels inappropriately high for the state of hydration.

Bartter and Schwartz (1967) reviewed the clinical situations in which SIADH has been reported. These included malignant tumours of bronchus, gut and thymus; neurological disorders, for example meningitis, trauma, subarachnoid haemorrhage and intracranial tumours; bacterial lung infections; and drugs. Interestingly they drew attention to the idea that secretion of ADH might possibly play a role in the development of the hyponatraemia of Addison's disease. In the case reported the clinical and biochemical features met the criteria of SIADH both before and after corticosteroid replacement except that prior to steroid treatment the patient was hypoadrenal. It is likely that psychotic symptoms were initially due to water overload. The patient was not clinically dehydrated and transiently lost weight following steroid treatment. The continuation of ADH hypersecretion following corticosteroid replacement was possibly due to failure to reset volume and osmoreceptors following sodium repletion. It is thought that this led to volume overload, accounting for the relapse of psychosis with features of sub-acute confusional state, and supported by the regain of body weight.

Various treatments of SIADH have been proposed. These include hypotonic saline, fluid restriction (Bartter, 1967), frusemide (Decaux, 1981), urea (Decaux, 1981), and demethylchlortetracycline (Forrest, 1978). Rapid reversal of the symptoms of psychosis and biochemical features of SIADH in our patient was achieved by demethylchlortetracycline. The mechanism of action of this drug is by interfering with the cyclic AMP-mediated action of ADH at the level of the distal renal tubule cells, acting either by inhibiting cyclic AMP formation or its action (Singer, 1973).

No cause for the later recurrence of psychosis with elevated ADH level was found. In particular, it was not related to omission or excess corticosteroids. ADH may be released by phenothiazines but at the time of this relapse, the patient was not taking phenothiazines. This relapse may possibly denote an incipient schizophrenic illness.

It may be argued that the association between psychosis on three occasions and endocrine abnormalities might have been coincidental. However, three aspects of this case of not support this contention. First, the clinical picture of psychosis developed *pari passu* with the physical symptoms of hypoadrenalism. Secondly, the initial disappearance of psychotic symptoms occurred during treatment with corticosteroids alone. Thirdly, relapse of psychotic symptoms after the development of SIADH was completely and rapidly reversed by demethylchlortetracycline.

The relationship between water and electrolyte imbalance and altered mental state is well-recognised. Crammer (1959) found an inconsistent relationship between body weight, water and electrolytes and mood in two manic depressive patients. In the first weight loss accompanied the onset of depression, and in the second, weight loss accompanied the emergence from depression into hypomania. In these two patients weight loss was associated with increased urinary excretion of sodium, and weight gain with sodium retention. Such conflicting findings in the relationship between mental state and water and electrolyte balance led Crammer to conlude that both these biochemical and mental disturbances may be the result of a common neurological lesion rather than being directly related.

In our patient both weight loss and weight gain were associated with psychosis before and after steroid replacement respectively. His subsequent follow-up has not been characterised by fluctuation in body weight. C.T. scan and EEG were both normal excluding a macroscopic neurological lesion.

The mental state in SIADH comprising lassitude, delirium and coma, resembles that attributed to untreated Addison's disease. In this case persistent ADH secretion and symptoms of water intoxication associated with recurrent psychosis were present. Thus increased ADH secretion may contribute more commonly than has been previously recognised to the mental symptoms of Addison's disease.

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*E. G. Lever, M.R.C.P., *Senior Registrar, Department of Medicine, King's College Hospital, Denmark Hill, London SE5*

S. A. Stansfeld, M.R.C.Psych., M.R.C.P., *Registrar, Bethlem Royal and Maudsley Hospitals; Current Appointment: Research Worker, General Practice Research Unit, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5*

*Reprint requests.

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