other than metoclopramide and, in particular, had not received aspirin. There was a past history of asthma controlled in recent years by inhaled salbutamol. On admission he was vomiting, confused and irritable. Except for typical varicella skin lesions and clinical evidence of dehydration, there were no abnormal signs. Intravenous normal saline was given. After a few hours combative behaviour necessitated sedation with intravenous diazepam and chlor-methiazole. At this time bilateral extensor plantar responses were found. CT head scan and CSF examinations were carried out. Intravenous fluids were continued but no other medication was given. By the following day he was alert, cooperative and orientated and without abnormal neurological signs. A prompt and complete recovery was made and he remained well two months later.

Initial hospital investigation gave the following results: haemoglobin 16.4 g/dl, white cell count $12,200 \times 10^9/l$ (62% polymorphs, 36% lymphocytes), platelet count $47,000 \times 10^9/l$, plasma glucose 6.1 mmol/l, urea 8.1 mmol/l, sodium 142 mmol/l, potassium 3.5 mmol/l; total bilirubin 13 $\mu\text{mol/l}$, aspartate aminotransferase activity 165 IU/l (normal 13–38), alkaline phosphate activity 396 IU/l (adult range 75–245) and plasma ammonia 248 $\mu\text{mol/l}$ (normal range 10–47). Clotting studies were normal. Two days later the platelet count was normal and the sole biochemical abnormality was aspartate aminotransferase activity 395 IU/l. Lumbar puncture on the second day of admission gave an opening pressure of 230 mm of water. The CSF contained no cells and protein content was 150 mg/l. CT head scan was normal. EEG performed on the third day of admission showed a mild bilateral excess of theta activity. Serum CFT to varicella zoster was positive at a titre of 1:320. Convalescent biochemical tests, including aspartate aminotransferase, were normal.

Perhaps due to wider recognition of the condition, mild cases of Reye's syndrome in children have been noted with increasing frequency.⁸ This case associated with an otherwise uncomplicated varicella infection indicates that mild cases also occur in adults. We suspect that Reye's syndrome may go unrecognised and emphasise the importance of measuring plasma ammonia levels in cases of acute encephalopathy with profuse vomiting. Prompt diagnosis is important because the mitochondrial changes and metabolic defects are normally self-limiting⁹ provided that the systemic biochemical disturbances particularly

dehydration, hypoglycaemia and cerebral oedema, can be controlled.

BRF LECKY,* JB WINER and S KENWRIGHT†
The Department of Neurology,
Guy's Hospital, London SE1 9RT, and
Department of Medicine,
William Harvey Hospital,
Ashford, Kent,† UK

*Present address: Dr. Lecky, The National Hospitals for Nervous Diseases, Maida Vale, London, W9 1TL, UK

References

- 1 Reye RDK, Morgan G, Baral J. Encephalopathy and fatty degeneration of the viscera: a disease entity in childhood. *Lancet* 1963;2:749–52.
- 2 Sullivan-Bolyai JZ, Corey L. Epidemiology of Reye syndrome. *Epidemiologic Reviews* 1981;3:1–26.
- 3 Morse RS, Holmes AW, Levin S. Reye's syndrome in an adult. *Dig Dis Sci* 1975;20:1184–90.
- 4 Varma RR, Riedel DR, Komorowski RA, Harrington GJ, Nowak TV. Reye's syndrome in nonpediatric age groups. *JAMA* 1979;242:1373–5.
- 5 Atkins JN, Haponik EF. Reye's syndrome in the adult patient. *Am J Med* 1979;67:672–8.
- 6 Vanholder R, De Reuck J, De Coster W. Reye's syndrome in an adult. *Eur Neurol* 1979;18:367–72.
- 7 Davis LE, Kornfield M. Influenza A virus and Reye's syndrome in adults. *J Neurol Neurosurg Psychiatry* 1980;43:516–21.
- 8 Lichtenstein PK, Heubi JE, Daugherty CC, et al. Grade I Reye's syndrome. *N Eng J Med* 1983;309:133–9.
- 9 Partin JS, McAdams AJ, Partin JC, Schubert WK, McLaurin RL. Brain ultrastructure in Reye's disease. II. Acute injury and recovery processes in three children. *J Neuropathol Exp Neurol* 1978;37:796–819.

Accepted 18 February 1984

Thiazides, compulsive water drinking and hyponatraemic encephalopathy

Sir, Compulsive water drinking frequently defies diagnosis until the patient develops hyponatraemic encephalopathy. This complication most often arises when normal homeostatic mechanisms are deranged.¹ When such mechanisms are preserved, additional factors must be sought, one of which is the use of a thiazide diuretic.^{1,2} To our knowledge, there have been 11 detailed case reports of hyponatraemic

encephalopathy in patients with compulsive water drinking taking a thiazide diuretic.^{1–7} The infrequency of this association was felt to merit a further addition to this literature.

A 48-year-old female was admitted to hospital in 1982 with a 7 day history of progressive confusion and restlessness. She had a 20 year history of alcohol abuse. In 1972 she underwent uncomplicated aneurysm surgery for subarachnoid haemorrhage. Four years later she had a single generalised seizure, since when she had taken phenobarbitone 90 mg per day. For one year she had taken Moduretic (hydrochlorothiazide 50 mg and amiloride hydrochloride 5 mg) 1 tablet per day for hypertension. On admission, she was restless, irritable and disorientated. There were no psychotic features. Physical examination was unremarkable. A provisional diagnosis of alcohol withdrawal was made and diazepam, 15 mg per day, and multivitamins were prescribed. The Moduretic and phenobarbitone were continued. Within 2 days her abnormal mental state had resolved, at which time blood biochemistry was normal.

Three weeks after admission, she complained of insatiable thirst and was noted to be drinking large volumes of water. Symptoms of headache and vomiting were followed by confusion, coma and a single seizure. At this time the serum sodium was 119 mmol/l; the potassium 3.3 mmol/l; the chloride 81 mmol/l; the creatinine 164 $\mu\text{mol/l}$; and the urea 4.9 mmol/l. The plasma osmolality was 237 mOsm/kg H_2O with coincident urine osmolality of 169 mOsm/kg H_2O , urine sodium of 24 mmol/l and urine potassium of 17 mmol/l. Other relevant investigations⁸ were normal. Moduretic was discontinued and phenytoin, 300 mg per day, was added. Phenobarbitone was withdrawn 4 days later. Restriction of water intake resulted in rapid clinical recovery and return of biochemical parameters to normal. Shortly thereafter, a further episode of excessive water drinking occurred. Intake was restricted and there were no sequelae. Five weeks later she was discharged on phenytoin, 300 mg per day, having displayed no further desire to drink excessively.

There are at least three mechanisms whereby thiazides could have contributed to the hyponatraemia in our patient and the 11 other reported cases.^{1–7} First, as a direct consequence of natriuresis. Second, as a result of reduced free water clearance. These mechanisms may have greatest relevance to the three patients who developed

Letters

hyponatraemic encephalopathy within 1 week of taking thiazides,^{5,6} since (with a constant intake) an "escape" from negative sodium balance can occur after 5 days of constant thiazide administration.¹⁰ Finally, thiazides have been implicated as a cause of the syndrome of inappropriate secretion of antidiuretic hormone.¹¹⁻¹³ In our patient and in seven of the previously reported cases,^{1,2,4,5,7} biochemical findings at the time of hyponatraemic encephalopathy were compatible with Syndrome of inappropriate secretion of antidiuretic hormone¹⁴ (though thiazides may have contributed directly to the urine tonicities⁹).

Fichman *et al*¹¹ proposed that thiazides stimulate release of antidiuretic hormone by extracellular volume contraction which in turn results from thiazide induced potassium depletion. Such a mechanism of antidiuretic hormone release may be specially important in the development of hyponatraemic encephalopathy in patients with compulsive water drinking, since Hariprasad *et al*¹⁵ recorded hypokalaemia in 17 of such patients who were *not* taking diuretics. Thus in the four patients^{1,5,7} who were known to have either continuous or periodic compulsive water drinking, the introduction of thiazides may have acted as a further stimulus to antidiuretic hormone release and have been the critical factor in precipitating hyponatraemic encephalopathy. Also, it may be relevant that in six of the reported cases,^{1,4-7} serum potassium was ≤ 3.0 mmol/l at the time of hyponatraemic encephalopathy. In our patient, however, other mechanisms seem likely since she was also taking a potassium sparing diuretic and the serum potassium was 3.3 mmol/l.

As in all previously reported cases (with one possible exception⁹) our patient had another illness or was taking another drug implicated in Syndrome of inappropriate secretion of antidiuretic hormone.⁸ Thus the precise role of thiazides in the development of hyponatraemic encephalopathy in these patients with compulsive water drinking remains uncertain. However, the very occurrence of such an association seems good reason to caution the use of thiazides in those patients at known risk for other causes of Syndrome of inappropriate secretion of antidiuretic hormone.

ROBIN A EMSLEY

Department of Psychiatry, Faculty of Medicine, University of Stellenbosch PO Box 63 Tygerberg, 7505 Cape, South Africa

RICHARD F GLEDHILL

Principal Neurologist, Senior Lecturer in Medicine, University of Stellenbosch, Tygerberg, 7505, South Africa

Present address: Lecturer, Department of Neurology, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF

References

- ¹ Kennedy RM, Earley LE. Profound hyponatremia resulting from a thiazide-induced decrease in urinary diluting capacity in a patient with primary polydipsia. *N Engl J Med* 1970;**282**:1185-6.
- ² Smith WO, Clark ML. Self-induced water intoxication in schizophrenic patients. *Am J Psychiatry* 1980;**137**:1055-60.
- ³ Langgagd H, Smith WO. Self-induced water intoxication without predisposing illness. *N Engl J Med* 1962;**266**:378-81.
- ⁴ Raskind M. Psychosis, polydipsia and water intoxication. *Arch Gen Psychiatry* 1974;**30**:112-4.
- ⁵ Beresford HR. Polydipsia, hydrochlorothiazide, and water intoxication. *JAMA* 1970;**214**:879-83.
- ⁶ Gossain VV, Hagen GA, Sugawara M. Drug-induced hyponatremia in psychogenic polydipsia. *Postgrad Med J* 1976;**52**:720-2.
- ⁷ Fowler RC, Kronfol ZA, Perry PJ. Water intoxication, psychosis, and inappropriate secretion of antidiuretic hormone. *Arch Gen Psychiatry* 1977;**34**:1097-9.
- ⁸ Robertson GL. Diseases of the posterior pituitary. In: Felig P, Baxter JD, Broadus AE, Frohman LA, eds. *Endocrinology and Metabolism*. New York: McGraw-Hill, 1981; Chapter 9: 251-77.
- ⁹ Earley LE, Orloff J. The mechanism of antidiuresis associated with the administration of hydrochlorothiazide to patients with vasopressin-resistant diabetes insipidus. *J Clin Invest* 1962;**41**:1988-97.
- ¹⁰ Goldberg M. The renal physiology of diuretics. In: Orloff J, Berliner RW, Geiger SR, eds. *Handbook of Physiology. Section 8, Renal Physiology*. Washington DC: Am Physiol Soc, 1973; Chapter 28:1003-31.
- ¹¹ Fichman MP, Vorherr H, Kleeman CR, Telfer N. Diuretic-induced hyponatremia. *Ann Intern Med* 1971;**75**:853-63.
- ¹² Husby S, Marthedal NJ. Hyponatremia due to a thiazide diuretic. *Acta Med Scand* 1981;**210**:523-4.
- ¹³ Hamburger S, Koprivica B, Ellerbeck E, Covinsky JO. Thiazide-induced syndrome of inappropriate secretion of antidiuretic hormone. *JAMA* 1981;**246**:1235-6.
- ¹⁴ Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med* 1976;**42**:790-806.
- ¹⁵ Hariprasad MK, Eisinger RP, Nadler IM, Padmanabhan CS, Nidus BD. Hyponatremia in psychogenic polydipsia. *Arch Intern Med* 1980;**140**:1639-42.

Accepted 10 March 1984