Missed Diagnosis

Recurrent confusion and hypopituitarism

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Summary: Three women in late middle age had recurrent episodes of confusion which could not be explained solely on the basis of an associated infection. All three patients had latent hypopituitarism diagnosed on final presentation. Each patient had a previous history of a severe postpartum haemorrhage followed by two further pregnancies.

Experienced clinicians had not made a diagnosis of confusional episodes due to hypopituitary encephalopathy because the history was not immediately available in the confused patient, and the significance of deficient axillary and pubic hair was not given due emphasis.

Introduction

Confusional states have many causes including infection. It is important to realize that the stress of infection may activate other latent factors causing a confusional state. These factors may require treatment, otherwise recurrent confusional episodes will follow. The present three cases are of postmenopausal women in whom recurrent confusional episodes could not be explained solely on the basis of associated infection. Latent hypopituitarism was diagnosed in each case on final presentation. This diagnosis had not been made previously by experienced clinicians because subtle signs had not been given due emphasis.

Case reports

Case 1

A 58 year old woman presented on three occasions over a period of 3 years with a history of confusion, neck stiffness and pyrexia. On the first two admissions a chest X-ray showed a lobar pneumonia. The remaining investigations were negative with the exception of low glucose levels in the plasma and cerebrospinal fluid (CSF) of 1.3 and 2.3 mmol/l, respectively. Treatment with antibiotics caused resolution of symptoms within 2 days, and she was discharged from hospital. On the third occasion

when she again presented with confusion, neck stiffness and pyrexia, it was noted that she had absent axillary and pubic hair. She also had a spastic paraparesis. CSF examination again showed a low glucose level, with 15 lymphocytes/ μ l (normal range $\leq 5/\mu$ l) and a normal protein. Electroencephalogram (EEG) showed generalized bilateral delta activity. Computed tomographic (CT) head scan was normal. A provisional diagnosis of viral encephalomyelitis was made on admission. She became lucid and co-operative after 5 days and said that a diagnosis of myxoedema had been made 17 years previously, and she had been maintained on replacement therapy with L-thyroxine. She had had a severe postpartum haemorrhage 28 years before, followed by two further pregnancies. Her menopause was 8 years prior to admission. Hypopituitarism was confirmed (Table I) and hydrocortisone replacement therapy was given in addition to thyroxine. Her EEG returned to normal.

Case 2

A 59 year old lady presented with three episodes of confusion, pyrexia, diarrhoea and vomiting within a period of 6 months. EEGs showed generalized delta activity on each occasion. On her third admission lumbar puncture showed a low CSF glucose (Table I); the remaining investigations which included a CT head scan were normal. The confusional episodes resolved within 2 days with intravenous fluid and antibiotics.

At the third admission absent axillary and pubic hair was noted, and a diagnosis of hypopituitary encephalopathy investigated. She had had a severe

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Accepted: 4 December 1992

postpartum haemorrhage after the first of three pregnancies. The menopause took place at the age of 49. Tests of pituitary function confirmed hypopituitarism (Table I). She was treated with hydrocortisone and thyroxine replacement. Her EEG had returned to normal 12 weeks later.

Case 3

A 64 year old woman presented with a history of confusion and diarrhoea on three occasions over a period of 10 months. *Bacillus subtilis* was grown from the stool on the first occasion and *Clostridium difficile* on the second. CSF examination and CT head scan were normal on the first and third admission. The EEG was abnormal with diffuse delta activity on each occasion, which resolved in 1–2 weeks. With intravenous fluids and antibiotics her confusional states recovered within 2 days. On her third admission absence of axillary and pubic hair was noted and the history was obtained of myxoedema, diagnosed 10 years earlier. She had been maintained on L-thyroxine. She also gave a history of severe postpartum haemorrhage after the fourth of six pregnancies. Her menopause had been at the age of 49. Hypopituitarism was confirmed (Table I).

There has been no recurrence of encephalopathy in any of these three patients since treatment was instituted.

Discussion

The patients described had recurrent attacks of confusion which could not be explained solely on the basis of an associated infection. In all three patients latent and unsuspected hypopituitarism was finally diagnosed. This diagnosis had not been made by experienced clinicians firstly because the history was not immediately available in the confused patient and secondly the significance of deficient axillary and pubic hair in postmenopausal women had not been given due emphasis.

Most routine investigations were essentially negative including plasma sodium levels although low CSF and plasma glucose levels might have led to consideration of a possible diagnosis of hypopituitarism and the EEG alerted the clinician to a metabolic encephalopathy as the cause of the confusional state. After three episodes of confusion in each patient a diagnosis of recurrent confusional episodes due to hypopituitary encephalopathy was confirmed by endocrine function tests.

Hypopituitary coma is generally well recognized and can pre- or postdate an associated psychosis.^{1,2} In the patients we have described the presentation was as a confusional state, they were not in coma, that is a state of unrousable unresponsiveness. A state of delirium has also been reported in hypopituitarism associated with pure cortisol deficiency,³ and a combined hypocortisol and

Table I Endocrinological verification of hypopituitarism

Test	Case 1	Case 2	Concentrations Case 3	Normal
Cortisol (acute state)	218	217	36	≥ 550 nmol/l
LST: cortisol				
0 minutes	32	—	5	
4 hours	699	—	196	> 1,000 nmol/l
24 hours	1,115	—	488	
9.00 am				
Cortisol	—	65	—	200–700 nmol/l
ACTH	—	< 2.3	—	2.3–18 pmol/l
Prolactin	230	120	210	< 80–280 mU/l
FSH	14	9.1	3	30–118 U/l
LH	10	5.8	4.2	16–66 U/l
FT4	18.2*	1.2	12.0*	11–29 pmol/l
TSH	0.7*	2.3	0.08*	0.3–6.2 mU/l
TRHT, TSH				
0 minutes	< 1.0			
30 minutes	1.5			
60 minutes	1.2			

*Whilst taking thyroxine. LST = Long Synacthen test, plasma cortisol measured just before (0 minutes), 4 hours and 24 hours after 1 mg of depot tetracosactrin intramuscularly; FSH = follicle stimulating hormone; LH = luteinizing hormone; FT4 = free thyroxine; TSH = thyroid stimulating hormone; TRHT = thyrotrophin releasing hormone (TRH) test, 200 µg of TRH given intravenously; failure of TSH response excludes primary hypothyroidism.

hypothyroid state,⁴ in these cases recovery took place only with specific hormone replacement.

In each of the present cases there was spontaneous recovery from two episodes of unrecognized hypopituitary encephalopathy causing confusion without specific hormone replacement. All three patients had subnormal LH and FSH levels and were cortisol deficient. Cases 1 and 3 were TSH deficient but on thyroxine replacement therapy. All cases had a history of severe postpartum haemorrhage which was responsible for their hypopituitarism. Postpartum pituitary necrosis (Sheehan's syndrome) is symptomatic when more than 70% of

the gland is destroyed.⁵ It is suggested that in the present cases postpartum haemorrhage caused subtotal or partial pituitary necrosis and that there was an additional age-related depression in pituitary function.

In conclusion, the patients described had recurrent hypopituitary encephalopathy activated by infection. Where confusional states occur which are not adequately explained by an infective illness, a metabolic encephalopathy and symptoms and signs of hypopituitarism should be sought (including the absence of axillary and pubic hair) and tests of endocrine function initiated.

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