Acta Med Scand 203: 231–235, 1978

Persistent Hypothalamic-Pituitary Insufficiency Following Acute Meningoencephalitis

A Report of Two Cases

Erik Hägg, Lennart Åström and Lars Steen

From the Department of Internal Medicine, University Hospital, Umeå, and the Department of Internal Medicine, County Hospital, Sollefteå, Sweden

ABSTRACT. This report concerns two patients, a 43-year-old woman and a 53-year-old man, who developed clinical as well as laboratory signs of permanent gonodal and thyroid failure following an acute intracranial infection—in the woman a meningoencephalitis of unknown origin, and in the man an encephalitis caused by Coxsackie B 5. Endocrine investigations were compatible with hypothalamic-pituitary dysfunction, with some of the results favoring a hypothalamic lesion. Perhaps hormone deficiency of hypothalamic and/or pituitary origin is a more common sequel of acute meningoencephalitis than has hitherto been reported.

Hypothalamic and pituitary insufficiency has diverse causes. In meningoencephalitis caused by microorganisms the hypothalamus and pituitary may be affected, but deficient hormonal secretion from these regions has not been reported very often and almost exclusively following tuberculous meningitis (cf. 21, 23). Hypothalamic-pituitary dysfunction, mainly diabetes insipidus, has been described in three neonates with meningitis caused by group B β-hemolytic streptococci (14, 18). Abramsky et al. (1) reported a 68-year-old man with transient diabetes insipidus as a complication of pneumococcal meningitis. In a review of 42 cases of diabetes insipidus, Jones (10) mentioned one patient with chronic meningitis and encephalitis of unknown origin, and three patients with syphilis, of whom two had evidence of disease of the central nervous system. Hypopituitarism has also been described in some patients with abscess formation in the pituitary region, sometimes associated with a pituitary tumor or as a complication of sphenoid sinusitis (cf. 7, 15). In addition, diabetes insipidus has been reported in a few cases of sinusitis without pituitary abscess formation (3, 27).

Since hypothalamic or pituitary hormonal deficiency, apart from diabetes insipidus, following acute non-tuberculous meningoencephalitis in adults does not appear to have been noticed in the literature, we considered it of interest to report two such cases.

ENDOCRINE STUDIES

Serum cortisol concentration was estimated by radioimmunoassay (Gammacoat, Clinical Assays, Inc.). Total thyroxine in serum was assayed by competetive protein binding technique (20) and thyrotrophin (TSH) in serum according to Odell et al. (17). Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH) and growth hormone (GH) were determined by radioimmunosorbent technique (24, 25). Serum testosterone level was assayed by radioimmunoassay (2). Porter-Silber chromogens and 17-ketosteroids in urine were measured by the methods of Silber and Porter (22) and Hamburger (9), respectively.

The insulin tolerance test was performed in the morning in fasting state and 0.10–0.15 U/kg of insulin was given i.v. In both patients the blood glucose concentration fell below 2.0 mmol/l, associated with profuse sweating. Blood for cortisol and GH assays was drawn at zero time and 15, 30, 60, 90 and 120 min after insulin administration. In vasopressin test, 10 IU of lysine-vasopressin (Postacon®) was given i.m. Serum cortisol concentration was determined before and 30 and 60 min after injection. Thyrotrophin-releasing hormone (TRH) and LH-releasing hormone (LH-RH) tests were performed as follows: 200 μg TRF (Roche) and 100 μg LH-RH (Hoechst) were given i.v. Blood samples for measurements of TSH and of LH and FSH respectively were taken before and 20 and 60 min afterwards.

Table I. *Serum hormone values in the patients*

	Normal values	Pat. 1	Pat. 2
Thyroxine (nmol/l)	79–158	52, 65, 54	36
Free thyroxine index	72–160	41, 53, 43	30
TSH (mU/l)	1.0–8.0	2.8–5.7	3.3, 5.2
Testosterone (μg/l)	♀ 0.40–0.80 ♂ 4.0–10.0	<0.11	2.1
LH (μg/l)	0.4–3.0	0.18	0.13
FSH (μg/l)	0.5–3.0	0.70	0.35

REPORT OF CASES

Case 1

The patient, a 43-year-old housewife with four children (the youngest born in 1970), has no family history of endocrine diseases. She had been essentially healthy until Dec. 26, 1972, when she fell acutely ill with headache, nausea and vomiting. On the following day, high fever (max. 39.4°C) and deterioration of vision occurred, and she was admitted to the Department of Internal Medicine at her local hospital.

The patient was somewhat drowsy on admission but lucid. Examination revealed normal eye grounds, central scotomas on both eyes with greatly impaired visual acuity, which was interpreted as retrobulbar neuritis. Except for these visual signs, the neurological examination was normal. Cervical rigidity, absent on admission, was noted two days afterwards. Repeated (three) lumbar punctures disclosed an increased pressure (285 mm of water) and a pleocytosis (almost 400 cells/mm^3) consisting mainly of polymorphonuclear cells. Protein content of cerebrospinal fluid was increased to 277 mg/100 ml and glucose concentration was slightly reduced (about 40 mg/100 ml). There was no xantochromia. Bacteria could not be detected on direct examination and cultures of spinal fluid for bacteria (including tubercle bacillus) and virus did not show any growth. EEG disclosed a slight, general abnormality. An X-ray of the skull was normal. Maximum ESR was 81 mm/hour.

The patient was treated with ampicillin, streptomycin, isoniazid and ACTH and a rather rapid amelioration occurred. The fever disappeared on the sixth day after admission. On the third hospital day urinary output was 5.5 l/24 hours. Urinary concentration power was not tested. Administration of vasopressin decreased the polyuria. When the patient left hospital after one month, she was feeling well, her visual impairment had greatly improved and EEG was normal. Treatment with streptomycin and isoniazid was continued for an additional month, but no further medication was given.

After the disease in Dec. 1972 the patient has had amenorrhea (last menstruation in Dec. 1972), libido has diminished and she has suffered from tiredness. In March 1973 paresthesias, weakness and edema of the hands started and a hypertension was detected with a peak value of 210/130 mmHg. The hypertension has been treated with propranolol (Inderal®) 80 mg twice daily since April 1974. In 1974 she gained approximately 10 kg and began to notice puffiness of her face and eyelids. When examined at the Medical Department of her local hospital during May-June 1973, the serum level of protein-bound iodine was low (2.7–2.8 μg/100 ml). Serum LH concentration was 0.60 μg/l (near the lower border for women of fertile age) and serum FSH 0.90 μg/l (normal value). Urinary estrogen levels were very low (estrone+estradiol 1–2 μg/24 hours). Temporary oral treatment with conjugated estrogens (Promarit®) during 1975 did not induce menstrual bleeding. In the same year, treatment with levothyroxine sodium (Levaxin®, 0.1 mg/day) was given for 3 months, yet her symptoms did not disappear.

During 1976 the patient was further treated at the Department of Internal Medicine of the local hospital and of Umeå University Hospital. Physical examination revealed a moderate obesity and thinning of axillary hair but the skin was without abnormalities. The thyroid gland was not palpable. BP was normal without propranolol medication. Gynecological examination was uneventful and a routine neurological investigation was normal. Examination of the ocular fundi showed a slight pallor of the optic discs and there was a homonymous left lower quadrantic anopia. X-ray examination of the pituitary fossa and EMI-scanning of the brain were normal.

ESR varied between 21 and 38 mm. Hb concentration was normal. Serum levels of sodium, potassium and creatinine were normal. An oral glucose tolerance test was within normal limits. Basal metabolic rate was −18%. Cholesterol value in serum was 7.0 mmol/l. Antithyroglobulin antibodies could not be detected in the serum. Urinary osmolality was normal under water deprivation (960 mosm/kg).

As shown in Table I, the patient had low values of both serum thyroxine and free thyroxine index. Serum TSH level was normal and after TRH administration (Table II) TSH showed a normal rise but with a tendency to a delayed response. During the insulin tolerance test the peak serum cortisol value was on the low side, in contrast to the quite normal elevation during the vasopressin test. Hypoglycemia did not induce any significant increase in serum GH concentration. Urinary excretion of Porter-Silber chromogens was normal (about 15 μmol/24 hours) but the urinary content of 17-ketosteroids showed low borderline levels (about 10 μmol/24 hours). Serum testosterone and LH concentration were significantly reduced. There was a significant increase in both LH (of 159%) and FSH serum levels (of 67%) 60 min after LH-RH administration.

Substitution therapy has just started (with cortisone acetate, levothyroxine sodium, estradiol and norethisterone) and therefore the effects of this treatment cannot yet be evaluated.

Case 2

A 53-year-old foreman with no heredity for endocrine disorders. Apart from nasal polyps he had been well. In the beginning of Oct. 1973 the patient complained of a severe headache, nausea, vomiting and high fever (39.3°C)

Table II. *Effect of hypoglycemia, vasopressin and TRH on serum cortisol, GH and TSH levels in the patients*

	Normal values	Pat. 1	Pat. 2
Insulin tolerance test			
Cortisol (nmol/l)			
Basal level	>280	228	322
Peak level	>600	539	751
GH (μg/l)			
Basal level	<5	0.64	<0.52
Peak level	>10	1.14	0.68
Vasopressin test			
Cortisol (nmol/l)			
Basal level	>280	457	
Peak level	>500	844	
TRH test			
TSH (mU/l)			
0 min	TSH	4.0	5.2
20 min	increase	10.7	14.3
60 min	2–25	12.7	14.6

and was treated at home by the general practitioner. After 6 days, doxycycline (Vibramycin®) was given orally and the patient improved.

In the beginning of Nov. an intensive headache reappeared and the patient was admitted to the Department of Infectious Diseases at Umeå University Hospital. On admission his mental state was unaffected. Routine neurological examination disclosed no gross abnormality and there was no cervical stiffness. The ocular fundi were normal. Lumbar puncture revealed normal pressure (130 mm of water), a clear, colourless cerebrospinal fluid with 14 mononuclear cells/mm³ and a slightly increased protein concentration (59 mg/100 ml). Spinal fluid cultures were positive for Coxsackie B 5.

A few days after admission his temperature rose from about 37°C to 38.5°C, and the patient complained of double vision. A sixth nerve paresis of both eyes was found. EEG revealed a slight, unspecific abnormality over the posterior parts of both hemispheres. Both echoencephalography and skull X-ray were normal except for a thickening of the lining membranes of the right maxillary sinus and of the ethmoid cells. ESR was 56–24 mm/hour.

Treatment began with oral azidocillin (Globacillin®) and nose drops and the patient improved. He left hospital after nearly four weeks, and after an additional three months the diplopia had disappeared completely.

Since the disease in 1973 the patient has suffered from tiredness. In 1975 he also noticed intolerance to cold, dryness of the skin, decreased sweating and disappearance of hair on the trunk and extremities. Furthermore, libido decreased and ejaculation was abolished. In April 1974 serum thyroxine level was somewhat low, 66.8 nmol/l, as was the free thyroxine index, 41. Serum TSH concentration was normal, 5.2 mU/l. In 1975 he had an episode of bacteriuria and was treated with antibiotics.

In 1976 the patient was referred to the Department of Internal Medicine at Umeå University Hospital by the general practitioner because of low blood Hb level (about 100–110 g/l). On admission his general condition was good. Body hair was reduced in the axillae and the pubic region. The skin was pale, somewhat dry and atrophic. There was no gynecomastia. The thyroid gland was not palpable. The pulse was slow (50/min) and the BP 145/90 mmHg. The testes and the prostate were of normal size. A thorough neurological examination did not disclose anything abnormal. Ocular fundi, visus and visual fields were normal. X-ray of the skull showed a normal pituitary sella. The patient did not consent to an EMI-scanning of the brain. I.v. pyelography was normal except for one small stone (1×2 mm) on both sides, located in the renal papillae.

ESR was 32–23 mm/hour and Hb level 110 g/l. Serum iron concentration was within normal limits. Cholesterol value was 10.8 mmol/l. Test for antihyroglobulin antibodies was negative. Serum sodium, potassium, calcium and phosphate concentrations were normal. Serum creatinine value was somewhat increased, 113 μmol/l. Urinary concentration ability was reduced to 650 mosm/kg. The urine contained increased amounts of leucocytes, though bacterial urine cultures were negative.

Serum level of thyroxine and free thyroxine index were low (Table I). Basal serum TSH concentration was normal, as was the rise of TSH after TRH administration (Table II) except for a tendency to delayed response. During the insulin hypoglycemia test the increase in serum cortisol level was normal but there was no significant rise of serum GH concentration. Serum testosterone, LH and FSH levels were all low. However, the increase in LH (of 262%) and in FSH values (of 51%) 60 min after LH-RH administration appears to be essentially normal (26). Urinary excretion of Porter-Silber chromogens was normal, 10–25 μmol/day, but the excretion of 17-ketosteroids showed low borderline levels, 11–15 μmol/day.

The patient was treated with levothyroxine sodium (Levaxin®) and injections of testosterone (Testoviron-Depot®) with a marked improvement of his symptoms.

DISCUSSION

The woman presented here thus showed clinical and laboratory signs of gonadal and thyroid insufficiency. There were also laboratory findings of deficient secretion of GH and of a slightly impaired hypothalamic-pituitary-adrenal system. In addition, the patient had clinical signs of a transient diabetes insipidus during the acute illness. It is beyond doubt that these hormonal abnormalities were caused by the preceding acute meningoencephalitis, which, in accordance with her visual impairment, engaged the basal portions of the brain. The causative agent of the infection is not known but might probably be of viral origin.

The male patient had an encephalitis caused by Coxsackie B 5. Following this infection he de-

veloped signs of hypogonadism and of thyroid failure. He also had impaired GH secretion during insulin tolerance test but an intact hypothalamic-pituitary-adrenal axis.

As to the localization of the lesion causing deficient hormonal secretion in these two patients, the results of the TRH test favor a hypothalamic rather than a pituitary lesion. The typical response during a TRH test in patients with hypothalamic lesions is a rise of serum TSH but of a delayed type, i.e. the 60-minute level is higher than the 20-minute level (8). Patients with pituitary hypothyroidism typically show an impaired or absent response (8, 11). However, the TRH test does not seem to be entirely reliable in distinguishing between hypothalamic and pituitary hypothyroidism, since some patients with pituitary tumors and hypothyroidism have shown a dalayed or even a normal response to TRH (5, 12, 19). A normal rise of serum cortisol values during hypoglycemia (as in insulin tolerance test) implies an intact hypothalamic-pituitary-adrenal system (4). Consequently, patients with hypothalamic lesions may show an insufficient increase in cortisol during the insulin hypoglycemia test. On the other hand, such patients can exhibit a normal rise of serum cortisol levels during a vasopressin test (4). This was the situation of our female patient, which might indicate a predominantly hypothalamic lesion. The LH-RH test does not appear to be able to differentiate between hypothalamic and pituitary causes of hypoganadism (6, 13, 16).

Concerning the time relationship between the intracranial infection and the commencement of endocrine dysfunction, our both patients had laboratory signs of thyroid failure within six months after infection. In addition, the woman has had persistent amenorrhea following the meningoencephalitis and showed very low values of urinary estrogens five months after the infection.

It is not known how often hormonal deficiencies occur during and after an acute meningoencephalitis but it is reasonable to assume that the incidence may vary with the type of causative agent as well as with the extent of the brain lesion. Both patients reported here had neurological symptoms from the basal regions of the brain. It is possible that only those patients with meningoencephalitis giving focal neurological symptoms will develop hormone dysfunction. It may be that hypothalamic-pituitary dysfunction is a more common sequel of acute meningoencephalitis than is reflected in the literature and that the clinical picture of some patients with endocrine insufficiency perhaps might be misinterpreted as an ordinary postencephalitic syndrome.

REFERENCES

1. Abramsky, O., Soffer, D. & Marks, E. S.: Diabetes insipidus as a complication of pneumococcal meningitis. J Am Geriatr Soc 21: 232, 1973.
2. Bäckström, T., Damber, J.-E., Lindgren, S. & Carstensen, H.: The influence of lipid material and cross-reaction in radioimmunoassay of estrogen and testosterone without chromatography. Submitted to J Steroid Biochem.
3. Ball, K. P. & Thackray, A. C.: Diabetes insipidus due to sphenoidal sinusitis. Lancet 1: 637, 1948.
4. Edwards, C. R. W. & Besser, G. M.: Diseases of the hypothalamus and pituitary gland. Clin Endocrinol Metabol 3: 475, 1974.
5. Faglia, G., Peccoz, P. B., Ambrosi, B., Ferrari, C. & Neri, V.: Prolonged and exaggerated elevations in plasma thyrotropin (HTSH) after thyrotropin releasing factor (TRF) in patients with pituitary tumors. J Clin Endocrinol Metab 33: 999, 1971.
6. Franchimont, P., Demoulin, A. & Bourguignon, J. P.: Clinical use of LH-RH test as a diagnostic tool. Horm Res 6: 177, 1975.
7. Götze, P. & Kühne, D.: Hypophysenabszess mit rezidivierender Meningitis als Leitsymptom (präoperative Diagnose). Nervenarzt 46: 208, 1975.
8. Hall, R., Ormston, B. J., Besser, G. M. & Cryer, R. J.: The thyrotrophin-releasing hormone test in diseases of the pituitary and hypothalamus. Lancet 1: 759, 1972.
9. Hamburger, Ch.: "Micro-methods" for the determination of 17-ketosteroids in urine. Acta Endocrinol 1: 375, 1948.
10. Jones, G. M.: Diabetes insipidus. Clinical observations in forty-two cases. Arch Intern Med 74: 81, 1944.
11. Karlberg, B. & Almqvist, S.: Clinical experience with the thyrotrophin releasing hormone (TRH) stimulating test in patients with thyroid, pituitary and hypothalamic disorders. Acta Endocrinol (Kbh) 72: 697, 1973.
12. Karlberg, B., Almqvist, S. & Werner, S.: Effects of synthetic pyroglutamyl-histidyl-proline-amide on serum levels of thyrotrophin, cortisol, growth hormone, insulin and PBI in normal subjects and patients with pituitary and thyroid disorders. Acta Endocrinol (Kbh) 67: 288, 1971.
13. Marshal, J. C.: Investigative procedures. Clin Endocrinol Metabol 4: 545, 1975.
14. McReynolds, E. W. & Roy, S.: Diabetes insipidus secondary to group B beta streptococcal meningitis. J Tenn Med Assoc 117: 117, 1974.
15. Mohr, P. D.: Hypothalamic-pituitary abscess. Postgrad Med J 51: 468, 1975.
16. Mortimer, R. H., Fleischer, N., Lev-Gur, M. & Freeman, R. G.: Correlation between integrated LH

and FSH levels and the response to luteinizing hormone releasing factor (LRF). J Clin Endocrinol Metab 43: 1240, 1976.
17. Odell, W. D., Rayford, P. L. & Ross, G. T.: Simplified, partially automated method for radioimmunoassay of human thyroid-stimulating, growth, luteinizing, and follicle stimulating hormones. J Lab Clin Med 70: 973, 1967.
18. Pai, K. G., Rubin, H. M., Wedemeyer, Ph. P. & Linarelli, L. G.: Hypothalamic-pituitary dysfunction following group B beta hemolytic streptococcal meningitis in a neonate. J Pediatr 88: 289, 1976.
19. Pickardt, C. R., Geiger, W., Fahlbusch, R. & Scriba, P. C.: Stimulation der TSH-Sekretion durch TRF-Belastung bei hypothalamischen und hypophysären Krankheitsbildern. Klin Wochenschr 50: 42, 1972.
20. Seligson, H. & Seligson, D.: Measurement of thyroxine by competetive protein binding. Clin Chim Acta 38: 199, 1972.
21. Sherman, B. M., Gorden, Ph. & di Chiro, G.: Post-meningitic selective hypopituitarism with suprasellar calcification. Arch Intern Med 128: 600, 1971.
22. Silber, R. H. & Porter, C. C.: The determination of 17,21-dihydroxy-20-ketosteroids in urine and plasma. J Biol Chem 210: 923, 1954.
23. Toublanc, J.-E., Rougerie, J., Leraillez, J. & Bach, Ch.: Hypopituitarisme avec diabète insipide après meningite tuberculeuse. Découverte opératoire de deux tuberculomes. Arch Franç Péd 31: 797, 1974.
24. Wide, L., Axén, R. & Porath, J.: Radioimmunosorbent assay for proteins. Chemical couplings of antibodies to insoluble dextran. Immunochemistry 4: 381, 1967.
25. Wide, L., Nillius, S. J., Gemzell, C. & Roos, P.: Radioimmunosorbent assay of follicle-stimulating hormone and luteinizing hormone in serum and urine from men and women. Acta Endocrinol (Kbh) (Suppl) 174, 1973.
26. Wollesen, F., Swerdloff, R. S. & Odell, W. D.: LH and FSH responses to luteinizing-releasing hormone in normal, adult, human males. Metabolism 25: 845, 1976.
27. Yaskin, J. C., Lewey, F. H. & Schwarz, G.: Diabetes insipidus and other unusual complications of acute purulent sinusitis. Clinicopathologic study of a case. Arch Neurol Psychiat 48: 119, 1942.