TSH and PRL response to thyrotrophin-releasing hormone in children with chronic renal failure undergoing haemodialysis

KUNLE IJAIYA

Department of Paediatrics, University of Cologne

SUMMARY Eight children (aged between 8½ and 15½ years) with chronic renal failure receiving intermittent haemodialysis, and 2 children with renal transplants were studied. The response of TSH and prolactin (PRL), and basal T4 and T3 values was measured. Basal TSH was normal, and rose only slightly after TRH stimulation. Plasma T4 and T3 were below normal levels in 6 children. Mean basal PRL was raised and could not be stimulated by TRH. This study demonstrates the involvement of the hypothalamus and pituitary in chronic renal disease. The cause of the abnormal secretion of TSH and PRL in chronic renal failure is discussed in the light of clinical importance.

Pituitary, thyroid, and gonadal hormones are important in the growth, skeletal, and sexual maturation of children. Endocrine abnormalities have been reported in patients with chronic renal failure (Feldman and Singer, 1975), in whom synthesis, secretion, and degradation of the affected hormones and their activity on target organs are impaired. In uraemic children, endocrine abnormalities have been observed by Czernichow *et al.* (1976) and Ijaiya *et al.* (1978), but information in this age group is scanty.

The present study was undertaken to assess hypothalamic and pituitary functions in children with chronic renal disease.

Patients and methods

Eight children with chronic renal failure (CRF) undergoing haemodialysis for 1 to 86 months, and 2 children who had had successful renal transplants 25 and 44 months earlier were investigated. Clinical details are shown in Table 1. Haemodialysis was generally performed for 6 hours 3-times a week.

No child showed galactorrhoea or gynaecomastia and no thyroid disease had been diagnosed. The aims of the study were explained to the patients and their parents and their informed consent was obtained. 22 (12 girls and 10 boys) healthy children, aged between 8 and 15 years, in hospital because of their short stature served as a control group. Five of these children have achieved almost complete sexual maturation, the rest were prepubertal. They were in

Department of Paediatrics, Ahmadu Bello University, Zaria
KUNLE IJAIYA, reader

Table 1 Clinical data of 8 children with chronic renal failure and 2 children with renal transplants

Case	Sex	Age (years)	Pubertal status*	Bone age† (years)	Height (cm)	Diagnosis	Haemodialysis treatment (months)	Other treatment
1	F	15.6	Stage 3	15	144	Chronic pyelonephritis	48	—
2	M	8.5	Stage 1	5	122	Haemolytic uraemic syndrome	10	—
3	M	9.0	Stage 1	7	124	Haemolytic uraemic syndrome	1	α-Methyldopa, reserpine, dihydrallazine
4	M	12.6	Stage 1	12	132	Oxalosis	12	Frusemide
5	F	15.2	Stage 3	15	147	Renal hypoplasia	86	—
6	F	12.8	Stage 1	11½	147	Polycystic kidney	22	—
7	F	15.1	Stage 2	13½	150	Chronic pyelonephritis	4	—
8	F	11.0	Stage 1	8	120	Glomerulonephritis	54	—
9	M	15.5	Stage 1	10	138	Megacystis-megaureter-syndrome	—	Renal transplant
10	M	14.2	Stage 1	7	134	Glomerulonephritis	—	Renal transplant

*Pubertal status rated according to Tanner and Whitehouse (1976), †bone age estimated according to Greulich and Pyle (1959).

good health and endocrine studies showed no abnormality.

Synthetic TRH (Relefact TRH, Hoechst AG, Frankfurt) was administered intravenously at a dose of 200 µg dissolved in 2 ml saline. All children were fasted overnight and remained in bed before and during the test. The test was performed at least 18 hours after haemodialysis. Blood samples were withdrawn through an indwelling cannula in an arm vein at 0, 15, 30, 45, 60, 90, and 120 minutes after TRH injection. Heparinised blood was immediately centrifuged at 4°C, and the plasma stored at -20°C until assayed for TSH, PRL, T4, and T3. Plasma TSH was determined by a double antibody radioimmunoassay (Utiger, 1965) (Amersham Buckler, Düsseldorf, Germany) (normal value, 0–7 µU/ml); plasma PRL by the double antibody method of Reuter *et al.* (1976) (Union Carbide, Sleoros, Belgium) (normal 6–10 ng/ml); plasma T4 by a competitive protein-binding radioassay (Res-O-Mat T4, Byck-Mallinckrodt Co, Dietzenbach, Germany) (normal 4.5–11.4 µg/100 ml), and T3 by radioimmunoassay (T3 RIA-KIT, Serono, Freiburg, Germany) (normal 0.6–1.7 ng/ml).

Statistical evaluations were by the Wilcoxon, Mann and Whitney U test for unpaired groups.

Results

Mean plasma concentration and SDs for basal TSH, PRL, T4, and T3 in controls and in children with CRF are shown in Table 2 which also shows the peak levels after TRH stimulation. The range of values and the results in the children with transplants are shown in Figs 1 and 2. No significant difference in basal levels of TSH, T4, or T3 was found. However, 6 of the 8 children with CRF had T3 or T4 levels below the normal range; PRL basal levels were significantly higher in the children with CRF failure. Basal levels were within the normal range in the children with transplants. After TRH stimulation, TSH rose in both groups with a peak response >8.0 µU/ml. In 5 cases TSH values had not fallen to basal levels 90 minutes after TRH injection. PRL levels

after TRH stimulation rose in the control children, but were not significantly different from basal levels in children with CRF. Case 3, who was receiving medication for acute hypertension (Table 1) and who had been on dialysis for only one month, had a normal basal PRL level (4.8 ng/ml) with only a slight rise after TRH. Sex, puberty, or duration of haemodialysis had no influence on the raised basal

Fig. 1 Serum TSH concentrations after IV TRH in 8 children with chronic renal failure and one child with transplant, compared with 22 healthy children. Range is shown as mean values $\pm$ SD.

Table 2 Mean plasma concentration (and SD) for basal serum TSH, prolactin, T4, and T3, and peak levels after TRH stimulation in controls and in children with chronic renal failure

Group	TSH (µU/ml)		PRL (ng/ml)		T4 (µg/100ml)	T3 (ng/ml)
	Basal	Peak	Basal	Peak	basal	basal
Controls (n = 22)	3.8 (2.3)	12.0 (4.2)	5.5* (2.9)	30.6 (11.1)	8.27 (2.23)	1.17 (0.23)
Chronic renal failure (n = 8)	4.5 (1.8)	9.8 (5.2)	17.8* (9.9)	21.4 (8.1)	5.98 (2.16)	0.59 (0.20)

* = U test $2\alpha < 0.05$.

Conversion: traditional units to SI—T4: 1 µg/100 ml $\approx$ 12.87 nmol/l, T3: 1 ng/ml $\approx$ 1.536 nmol/l.

Fig. 2 Concentration of serum PRL after IV TRH. Range is shown as mean values $\pm$ SD in 8 children with chronic renal failure and 2 children with successful renal transplants, compared with 22 healthy children.

level of plasma PRL, or on the failure to increase PRL concentration after TRH injection in children with CRF.

Discussion

Studies of thyroid function in patients with CRF have produced conflicting results; both hyperthyroidism (Schmidt *et al.*, 1971) and hypothyroidism with low T3 and T4 levels have been reported (Ramirez *et al.*, 1972; Czernichow *et al.*, 1976; Kølendorf *et al.*, 1978). Raised plasma-free thyroxine was reported by Bailey *et al.* (1967) in dialysed patients, and after successful renal transplants these parameters returned to normal. Heparin administration during haemodialysis raises levels of free T4, but not total T4 (Schatz *et al.*, 1969).

The thyroxine-binding capacity of TBG in chronic renal failure is normal (Joasso *et al.*, 1974; Kølendorf *et al.*, 1978), whereas the binding capacity of thyroxine-binding prealbumin is low (Jaffiol *et al.*, 1970). Joasso *et al.* (1974) suggested that the change

in serum T4 was due to some unidentified substance, which displaces T4 from TBG in serum of patients with renal failure. TSH, T4, and T3 are not dialysable (Bindeballe *et al.*, 1973; Silverberg *et al.*, 1973). Impairment of the peripheral conversion of T4 to T3 was also suggested (Lim *et al.*, 1977). Normal ^{131}I uptake after stimulation of thyroid with TSH in dialysed patients has been reported (Silverberg *et al.*, 1973).

Except in cystinosis, primary thyroid disease is unlikely to be responsible for the low levels of thyroid hormones (Burke *et al.*, 1978). TSH production might be expected to be stimulated by low levels of thyroid hormones, and raised basal value of serum TSH in dialysed patients has been reported (Waldhäusl *et al.*, 1971); others have found normal (Czernichow *et al.*, 1976) or low values (Silverberg *et al.*, 1973). Basal TSH was normal in our patients.

Despite low serum thyroid hormones and normal basal TSH level, exogenous TRH could not stimulate pituitary TSH release, suggesting a defect in pituitary secretion of TSH (Ramirez *et al.*, 1972; Silverberg *et al.*, 1973). The negative feedback mechanism seems, however, to be intact, for high dosages of T3 lowered TSH (Czernichow *et al.*, 1976). The cause of the pituitary abnormalities in these patients is unknown; severe malnutrition or uraemic toxins may be involved (D'Angelo, 1951; Feldman and Singer, 1975).

A trial of thyroid hormone replacement in dialysed uraemic patients with low serum T4 levels and clinical symptoms of hypothyroidism gave inconsistent results (Silverberg *et al.*, 1973). Chan *et al.* (1970) reported a 10-year-old boy with CRF and clinical signs of hypothyroidism who showed an increase in height velocity after starting thyroid extract. Increased growth velocity with thyroid supplementation occurred in only 2 out of 7 patients treated by Burke *et al.* (1978). An improvement in growth and better pubertal development may be achieved with thyroid hormone replacement.

An abnormal response of PRL to TRH, with raised basal PRL which could not be stimulated after TRH injection has been reported in uraemic patients (Czernichow *et al.*, 1976; Archer, 1977; Sciarra *et al.*, 1977). Despite the increased PRL, no galactorrhoea or gynaecomastia was observed. The high prolactin may be responsible for the hypogonadism or amenorrhoea in several patients (Thorner, 1977). Whether the hyperprolactinaemia in the uraemic child affects gonadal maturation, and therefore delay in puberty, needs further clarification. The cause and clinical importance of the raised PRL are still poorly understood. High PRL levels are found in primary hypothyroidism (personal observation) often combined with the triad galactorrhoea,

precocious puberty, and hypothyroidism (van Wyk and Grumbach, 1960). None of our patients exhibits clinical signs of hypothyroidism. The abnormal TSH response to TRH would even suggest a secondary hypothyroidism. In our patient receiving medication for acute hypertension PRL secretion was normal. This is despite the fact that several drugs—such as reserpine and α -methyldopa—have been found to increase serum PRL levels (Archer, 1977; Thorner, 1977).

The source of high PRL values in uraemic patients is still unknown. A loss of renal degradation cannot be the only cause, several other peptide hormones are not raised. Cowden *et al.* (1978) demonstrated a progressive rise in PRL concentrations as renal function deteriorates, and a return to normal after successful renal transplants. PRL is supposed to have a fundamental osmoregulatory role in many species of fish and amphibians (Lam, 1972). Its possible role as an osmoregulator in man remains controversial. The role of the hypothalamus and pituitary in the abnormal secretion of PRL is obscure. Since increased PRL secretion is due to a decrease in hypothalamic prolactin-inhibiting factor or an increase in prolactin-releasing factor (L'Hermite *et al.*, 1974), a dysfunction of the hypothalamus may result in decreased prolactin-inhibiting factor or increased prolactin-releasing factor biosynthesis or secretion.

This study has demonstrated the involvement of the hypothalamus and pituitary in children with CRF. Levels of T3 and T4 tend to be low and this is due to inadequate TSH production. PRL is high, but the pituitary reserve is limited so it does not rise further after TRH stimulation. The renal cause of the hypothalamic-pituitary dysfunction remains poorly understood.

This work was supported by the Deutsche Forschungsgemeinschaft, Bonn.

References

- Archer, D. F. (1977). Current concepts of prolactin physiology in normal and abnormal conditions. *Fertility and Sterility*, **28**, 125–134.
- Bailey, G. L., Hampers, C. L., and Merrill, J. P. (1967). Thyroid function in chronic renal failure (abstract). *Clinical Research*, **15**, 351.
- Bindeballe, W., Drenkhan, E., Jüsgen, W., Lahrtz, H., Leybold, K., Niedermayer, W., and Schemmeli, K. (1973). Influence of haemodialysis on hormone levels in preterminal renal failure (in German). *Deutsche medizinische Wochenschrift*, **98**, 661–665.
- Burke, J. R., El-Bishti, M. M., Maisey, M. N., and Chantler, C. (1978). Hypothyroidism in children with cystinosis. *Archives of Disease in Childhood*, **53**, 947–951.
- Chan, A. M., Lynch, M. J., Bailey, J. D., Ezrin, C., and Fraser, D. (1970). Hypothyroidism in cystinosis. *American Journal of Medicine*, **48**, 678–692.
- Cowden, E. A., Ratcliffe, W. A., Ratcliffe, J. G., Dobbie, J. W., and Kennedy, A. C. (1978). Hyperprolactinaemia in renal disease. *Clinical Endocrinology*, **9**, 241–248.
- Czernichow, P., Dauzet, M. C., Broyer, M., and Rappoport, R. (1976). Abnormal TSH, PRL, and GH response to TSH releasing factor in chronic renal failure. *Journal of Clinical Endocrinology and Metabolism*, **43**, 630–637.
- D'Angelo, S. (1951). The effect of acute starvation on the thyrotropic hormone level in the blood of the rat and mouse. *Endocrinology*, **48**, 341–343.
- Feldman, H. A., and Singer, I. (1975). Endocrinology and metabolism in uremia and dialysis. A clinical review. *Medicine*, **54**, 345–376.
- Greulich, W. W., and Pyle, S. I. (1959). *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. Stanford University Press: California.
- Ijaiya, K., Bulla, M., Roth, B., Gladtko, E., and Schwenk, A. (1978). Letter: Growth-hormone response to haemodialysis in children. *Lancet*, **2**, 573.
- Jaffiol, C., Baldet, L., and Mirouze, J. (1970). E'tude du transport plasmatique et du métabolisme des hormones thyroïdiennes dans le diabète sucré et diverses affections métaboliques. *Annales d'endocrinologie*, **31**, 350–362.
- Joasso, A., Murray, J. P. C., Parkin, J., Robertson, M. R., and Jeremy, D. (1974). Abnormalities of *in vitro* thyroid function tests in renal disease. *Quarterly Journal of Medicine*, **170**, 245–261.
- Køllendorf, K., Møller, B. B., and Rogowski, P. (1978). The influence of chronic renal failure on serum and urinary thyroid hormone levels. *Acta endocrinologica*, **89**, 80–88.
- Lam, T. J. (1972). Prolactin the osmoregulatory hormone in some fish and amphibian species—a review. *General and Comparative Endocrinology*, Supplement 3, 328–338.
- L'Hermite, M., Robyn, C., Goldstein, J., Rothenbuchner, G., Birk, J., Loos, U., Bonnyns, M., and Vanhaelst, L. (1974). Prolactin and thyrotropin in thyroid diseases: lack of evidence for a physiological role of thyrotropin-releasing hormone in the regulation of prolactin secretion. *Hormones and Metabolic Research*, **6**, 190–195.
- Lim, V. S., Fang, V. S., Katz, A. I., and Refetoff, S. (1977). Thyroid dysfunction in chronic renal failure. A study of the pituitary-thyroid axis and peripheral turnover kinetics of thyroxine and triiodothyronine. *Journal of Clinical Investigation*, **60**, 522–534.
- Ramirez, G., Jubiz, W., Gutch, C. F., and Kolff, W. J. (1972). Thyroid function in chronic renal failure. Effects of chronic hemodialysis. *Transactions; American Society for Artificial Internal Organs*, **18**, 244–247.
- Reuter, A. M., Kennes, F., Gevaert, Y., and Franchimont, P. (1976). Homologous radioimmunoassay for human prolactin. *International Journal of Nuclear Medicine and Biology*, **3**, 21–28.
- Schatz, O. L., Sheppard, R. H., Steiner, G., Chandrapaty, C. S., and de Veber, G. A. (1969). Influence of heparin on serum free thyroxine. *Journal of Clinical Endocrinology and Metabolism*, **29**, 1015–1022.
- Schmidt, P., Stobaeus, N., Prame, G., and Schitteck, F. (1971). Exophthalmos in chronic renal insufficiency. *Scandinavian Journal of Urology and Nephrology*, **5**, 146–153.
- Sciarra, F., Spurano, F., Giaquinto, G., Odoardi, A., Mercuri, M. A., and Concolino, G. (1977). Prolactinemia during haemodialysis: lack of correlation with sodium potassium and renin-aldosterone-system. *Hormone Research*, **8**, 129–138.
- Silverberg, D. S., Ulan, R. A., Fawcett, D. M., Dossetor, J. B., Grace, M., and Bettcher, K. (1973). Effects of chronic hemodialysis on thyroid function in chronic renal failure. *Canadian Medical Association Journal*, **109**, 282–286.
- Tanner, J. M., and Whitehouse, R. H. (1976). Clinical longi-

- tudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. *Archives of Disease in Childhood*, **51**, 170–179.
- Thorner, M. O. (1977). Disorders of prolactin secretion. *Journal of Clinical Pathology*, **30**, Supplement 7, 36–41.
- Utiger, R. D. (1965). Radioimmunoassay of human plasma thyrotropin. *Journal of Clinical Investigation*, **44**, 1277–1280.
- van Wyk, J. J., and Grumbach, M. M. (1960). Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism: an example of hormonal overlap in pituitary feedback. *Journal of Pediatrics*, **57**, 416–435.
- Waldhäusl, W., Schmidt, P., Frischauf, H., and Kotzaurek, R. (1971). Effect of thyrotropin releasing hormone (TRH) on HTSH and HGH in patients with chronic renal failure. *Proceedings of the European Dialysis and Transplant Association*, **8**, 161–166.

Correspondence to Dr K. Ijaiya, Department of Paediatrics, Ahmadu Bello University, Zaria, Nigeria.

Received 5 March 1979