Scand J Rehab Med 15: 43–46, 1982

GROWTH HORMONE AND PERIARTICULAR NEW BONE FORMATION—A CAUSAL RELATIONSHIP?

A Preliminary Communication

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ABSTRACT. In an attempt to examine the relationship between growth hormone (GH) and periarticular new bone formation (PNBF), we studied eight patients with brain lesions of different origins who were in a prolonged comatose state for 164 to 1320 days. Five of them developed PNBF. The latter reacted to both the specific L-Dopa test and to the non-specific TRH test with an increase in GH serum concentration. Those patients who did not develop PNBF, failed to react significantly to either tests. The difference in GH values between the two groups is statistically significant at the 95% level of confidence. We hypothesize that there may be a causal relationship between high concentrations of GH in serum and PNBF.

Key words: growth hormone, prolonged coma, PNBF

Periarticular new bone formation (PNBF) was first described by Dejerine & Celliers in 1918 (3). Relationships between PNBF and diverse processes such as spinal cord injury (3, 8), poliomyelitis (13), tetanus (14), carbon monoxide poisoning (2), burns (4), stroke (1, 11) and severe cerebral injuries (5, 6, 12) have been reported.

A few years ago we studied PNBF in a group of patients with cranio cerebral injuries, hospitalised at our intensive care unit, and suffering from prolonged coma. Since coma appeared to be a common denominator for all the patients, we suggested comatose status as a possible etiological factor for PNBF (5). At a later stage, we conducted a prospective study (12), describing the natural history of periarticular new bone formation. We could not find any relationship between this syndrome and factors such as patient, sex or age, etiology of the brain damage, duration or functional outcome of the comatose status.

Contradictory reports have suggested various etiological factors, without adducing sufficient supportive proof (6, 11). Factors mentioned included: long-term bedridden condition, paralysis, spasticity or trophic change in the limb affected, local trauma in joints affected or traumatic effect of physiotherapy.

Recently, Naejie (13) described elevated serum GH in barbiturate coma and a clear-cut rise after TRH administration, in patients with very short coma periods, between 48 and 105 hours. Since GH is unequivocally involved in bone formation (15) the study was performed to investigate whether adequate secretion of GH is a prerequisite for PNBF and can differentiate between those patients in prolonged coma who have PNBF and those who do not.

MATERIALS AND METHODS

This study described eight patients hospitalized at the Intensive Care Unit, following brain lesions of different origins, in prolonged comatose state which lasted from 164 to 1320 days. Their clinical data are shown in Table I.

The patients received a well-balanced diet by intragastric tube feeding. In an attempt to find radiographic evidence of PNBF, their shoulders, elbows, hips and knees were X-rayed bilaterally every 45 days. Patients who did not develop PNBF were radiographed for at least 14 months after injury (12). At the times of X-ray examinations and at different points during the observation period, calcium phosphate, phosphorus and alkaline phosphate levels in blood as well as urinary excretion of calcium and phosphorus were determined. No metabolic disturbances were found. All medication was stopped 14 days prior to and during specific hormonal tests. GH was measured using the GH RIA Kit supplied by Serona Laboratories, Milano, Italy (normal values 2 ng/ml). TRH test (22 mg) supplied by Roche was injected intravenously after 12 hours overnight fasting. Blood was drawn at 0, 15, 20, 60 and 120 min. L-Dopa test (500 mg) was given via nasogastric tube after overnight fast and blood was taken at 0, 45, 60 and 90 min.

The difference in GH secretion between Group A that

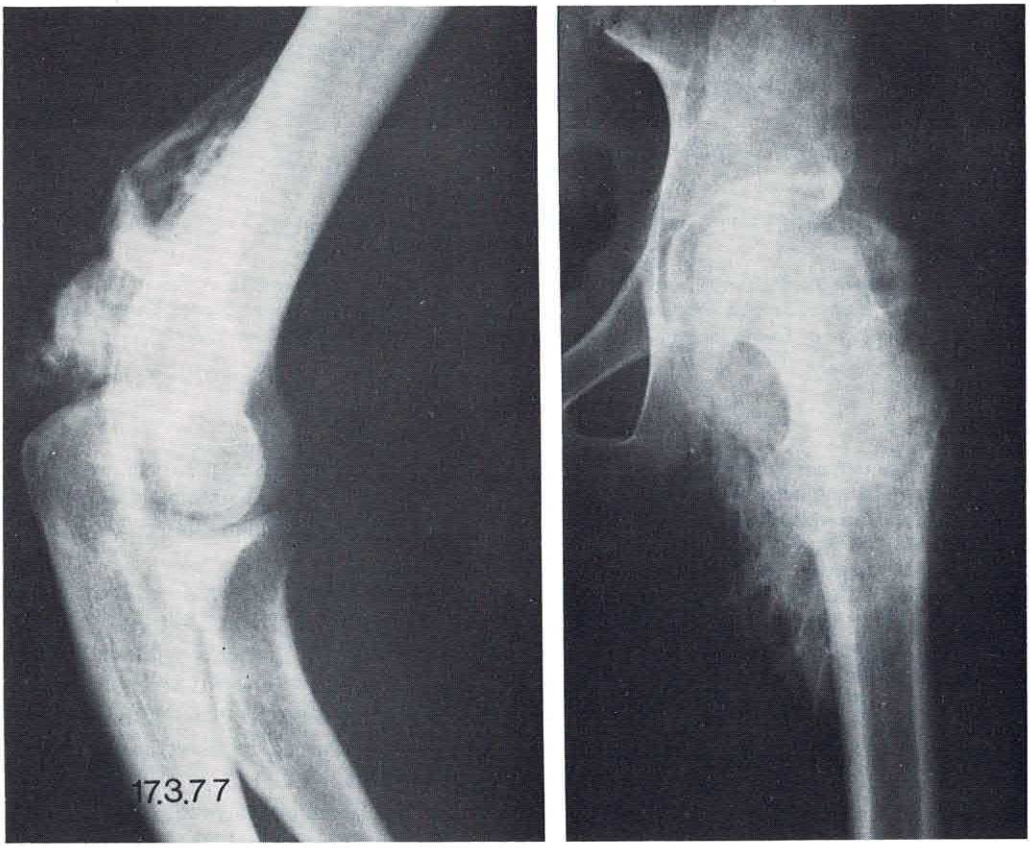

Fig. 1. Examples of PNBF in left elbow and left hip.

presents PNBF and Group B that does not, was tested. Both the one-tailed Student's *t*-test for independent samples, and the Fisher randomization two-sample *t*-test was performed. The latter obviates objections that might be held against the *t*-test in relatively small samples.

Table I. *Patients suffering prolonged coma. Population study*

Pat. no.	Sex	Age	Etiology of coma	Duration of coma (days)
1	M	25	Penetrating injury	1 320
2	M	23	Cerebral anoxia	471
3	M	29	Penetrating injury	1 247
4	M	16	Blunt injury	198
5	M	18	Blunt injury	164
6	M	18	Blunt injury	245
7	F	22	Cerebral anoxia	706
8	F	50	Cerebral anoxia	304

RESULTS

X-ray findings. Table II shows X-ray findings in 8 patients at the time hormonal tests were performed. Three traumatic patients and 2 non-trau-

Table II. *PNBF in latest X-rays of the 8 patients in prolonged coma as shown in Table I*

+ = affected joint

PNBF Pat. no.	Shoulder R	Shoulder L	Elbow R	Elbow L	Hip R	Hip L	Knee R	Knee L	Total
1	–	–	–	–	–	–	–	–	0
2	–	–	–	–	–	–	–	–	0
3	–	–	–	–	–	–	–	–	0
4	–	–	–	–	–	+	–	–	1
5	–	–	–	–	–	–	–	+	1
6	–	–	–	–	+	–	–	–	1
7	–	–	–	–	+	+	–	–	2
8	–	–	–	+	+	+	+	–	4

Table III. *Serum growth hormone concentration (ng/ml) after 500 mg L-Dopa*

Pat. no.	Time (minutes) 0	45	60	90
1	0.3	0.4	0.2	0.2
2	0.2	0.4	1.6	0.5
3	0.2	1.8	0.6	–
4	0.5	2.3	4.5	2.4
5	7.2	6.2	6.6	4.5
6	2.0	6.2	7.2	7.2
7	0.7	0.8	5.0	9.0
8	1.3	2.9	4.0	6.6

Table IV. *Serum growth hormone concentration (ng/ml) after 200 mg TRH*

Pat. no.	Time (minutes) 0	15	30	60	90	120
1	0.7	0.8	0.6	0.4	0.4	0.6
2	0.2	0.4	0.2	0.2	0.8	0.5
3	0.6	0.2	0.3	0.3	0.2	0.2
4	0.7	3.0	3.1	2.5	2.4	2.1
5	6.2	10.0	9.4	13.0	13.0	11.0
6	2.4	3.7	2.2	2.9	1.9	2.1
7	0.5	0.7	0.5	3.8	10.0	3.5
8	1.9	4.5	6.2	12.0	6.6	4.2

matic cases developed PNBF. The X-rays of two affected patients are present in Fig. 1.

Hormonal values. In the present study, basal serum growth hormone concentration was normal in all patients, except patient 5 who had a high basal level of GH on both tests (7.2 and 6.2 ng/ml respectively). Four of the comatose patients (nos. 4, 6, 7, 8) responded with an increase in GH serum after L-Dopa, to values equal or above 4.5 ng/ml during the test. One patient (no. 5) who had a high basal serum GH concentration did not show a rise, but all values were above 4.5 ng/ml. In three other patients (nos. 1, 2, 3) the serum GH concentration was less than 1.8 ng/ml during the test (Table III).

These three patients (Group B) (nos. 1, 2, 3) did not respond to the non-specific TRH test, while the other five patients (Group A) (nos. 4, 5, 6, 7, 8) showed a rise of at least 150% above basal level, and in three of them (nos. 5, 7, 8) the rise was to values as high as 6.6–13 ng/ml (Table IV). Glucose concentrations concomitant with TRH and L-Dopa test remained unchanged. Kidney and liver functions in all patients were normal.

The increase in GH concentration between basal levels and those at 60′ after L-Dopa, was greater in patients developing PNBF (Group A) compared with those who did not (Group B). Significance was at the 95% level ($p<0.05$) for both the Fisher and the Student's test.

DISCUSSION

There is no biological or physiological explanation for PNBF. The reason why 76.8% of 45 patients studied previously in prolonged coma developed PNBF and 23.2% did not has not been clarified. Both thyroid and growth hormone (GH) are essential for bone formation (15). In a previous study (10) we showed that in contrast to patients with relatively short coma (up to 33 days) (9), our population of patients in coma of more than 164 days had normal hypothalamic-pituitary-thyroid axis. Less is known about GH in comatose patients.

This study demonstrated clearly that serum GH concentration after both specific (L-Dopa) stimulation and non-specific stimulation (by TRH), was able to differentiate between the 5 patients in prolonged coma who developed PNBF and the 3 patients who did not. Therefore it seems that GH secretion is a prerequisite for PNBF. Further studies on somatomedin production may shed more light on this problem.

ACKNOWLEDGEMENT

We are grateful to Mr Yair Luz for his help in the statistical analysis.

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