NOTE

Effect of 1α OH-Vitamin D_3 in a Case of Pseudohypoparathyroidism

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Synopsis

A 37-year-old woman with typical features of pseudohypoparathyroidism (chronic tetany, paresthesia, persistent hypocalcemia, round face, short stature, short metacarpals and metatarsals, cutaneous calcification and lack of response to exogenous and endogenous parathyroid hormone as regards urinary phosphate and cyclic AMP excretion) was treated with oral administration of $2\mu\text{g/day}$ of 1α OH-vitamin D_3 . Serum calcium started to rise within 3 days returning to the normal level with disappearance of symptoms referable to hypocalcemia. Such a favorable effect of a small dose of 1α OH-vitamin D_3 in a patient with typical hypoparathyroidism suggests an important role of disturbance of 1α -hydroxylation of vitamin D_3 by the kidney in the pathogenesis of calcium and phosphorus abnormality in this disease. Forty-four cases of pseudohypoparathyroidism in the Japanese literature were briefly reviewed.

In addition to the classical remedies for hypoparathyroidism, vitamin D_2 and dihydrotachysterol, new vitamin D derivatives such as 1α OH-vitamin D_3 and $1,25(\text{OH})_2$ vitamin D_3 have recently been introduced in the treatment of various forms of hypoparathyroidism (Kooh *et al.*, 1975; Neer *et al.*, 1975), but few reports are yet available on the use of 1α OH-vitamin D_3 on pseudohypoparathyroidism (Sinha and Bell, 1976). We have experienced a typical case of pseudohypoparathyroidism with a prompt favorable response to 1α OH-vitamin D_3 .

Case Report

A 37-year-old woman was referred to

our Clinic in July 1975 with history of frequent attacks of tetany and hypocalcemia. The family history was free of hereditary disease or consanguineous marriage. Nothing abnormal occurred during pregnancy and on delivery. The growth in infancy was normal. A stiffening of the upper extremity due to tonic convulsion accompanied by a marked dyspnea but no loss of consciousness occurred for the first time when she experienced a severe emotional and physical stress of losing her home in a flood at the age of 15 years. For some time she had no similar attacks and was married at the age of 25 years, giving birth to one child next year and the child grew up normally. She suffered from rheumatoid arthritis and pyelonephritis at the age of 28. During the course of these diseases she suddenly became dyspneic at night and tracheotomy had to be performed. Attacks of paresthesia and tetany thereafter

Received for publication June 14, 1976.

This study was supported by a Research Grant from the Intractable Disease Division, Endocrine Receptor Disease Committee, Public Health Bureau, Ministry of Health and Welfare, Japan.

occurred 3 to 4 times a year and treated with intravenous injections of calcium salts. Serum calcium stayed in the range of 5.2 to 6.6 mg/dl over these years. No skin changes such as moniliasis were found. During the past several years attacks of tetany became less frequent with persistence of paresthesia. The level of serum calcium also became slightly higher, fluctuating around 6 to 7 mg/dl.

Physical examination revealed a slightly short, moderately fat woman 151 cm in height and 67 kg in weight. The face was round but head and body hairs appeared normal and no abnormal pigmentations were noted. Neither cataract nor papilledema was seen. Skull X-ray film revealed no intracranial calcification. Hard subcutaneous nodules were palpable on the anterior side of the right thigh and lateral side of both arms and the X-ray picture confirmed the presence of calcification in these areas. Chvostek's and Trousseau's signs were absent.

Laboratory tests revealed RBC 419×10^4 , WBC 4300 with normal differential count, ESR 13 mm/1 hour, serum total protein 7.3 g/dl, A/G ratio 1.35, BUN 20 mg/dl, creatinine 1.1 mg/dl, Na 142 mEq/l, K 3.5 mEq/l, Ca 7.2 mg/dl, P 4.5 mg/dl, alkaline phosphatase 8.2 King-Armstrong units, urinary Ca 56 mg/24 hours, urinary P 646 mg/24 hours under unrestricted diet, urine specific gravity in Fishberg's concentration test 1.023, 1.017 and 1.025, creatinine clearance 72 ml/min, PBI 5.4 μ g/dl, Trisorb Test 30.7% (normal range 25–40%), T_4 12.0 μ g/dl (normal range 6–12), urinary 17OHCS 2.9 mg/24 hours, urinary 17-KS 6.9–8.4 mg/24 hours, negative ECG, negative chest X-ray picture, and EEG with predominant θ waves. Glucose tolerance test revealed a flat curve and TmG was 230 mg/min and TmG/GFR 3.40 (normal range 2.50–3.00) (Halver, 1966). Roentgenological examination of the skeletal system indicated universally short metacarpals and

metatarsals especially the four I digits. Skull X-ray revealed no calcification of the basal ganglia or other abnormalities. Bone density was generally well maintained without evidence of demineralisation. Tubular reabsorption of phosphate (%TRP) was 84.6% (normal range $86.0 \pm 9.3\%$) and serum PTH was 0.7 ng/ml (normal range less than 0.6).

Intravenous injection of 200 USP units

Fig. 1. The Results of Ellsworth-Howard Test. The arrow indicates the intravenous injection of 200 USP units of Parathyroid Extract (Lilly). U_p/U_{cr} , urinary P excretion divided by urinary creatinine excretion (mg/hr) and UCAMP, urinary cyclic AMP excretion, are shown on the ordinate and time on the abscissa. Solid line represents the value in this patient and dotted line a normal control subject.

of Parathyroid Extract (Ellsworth-Howard test) resulted in 0.94-fold increase of urinary phosphate excretion compared to 2.14-fold increase in the normal control subject, indicating a negative phosphaturic response to exogenous parathyroid hormone. Urinary cyclic AMP determined by a radioimmunoassay also failed to increase (Fig. 1). Since EDTA rapidly induces hypocalcemia and subsequent PTH hypersecretion and urinary

cyclic AMP was shown to increase along with the severity of hypocalcemia in normal subjects probably reflecting PTH secretion (Drezner *et al.*, 1976), an EDTA test was carried out with intravenous infusion of 70 mg/kg Na₂-EDTA in 200 ml 5% glucose solution over a period of 20 min to induce endogenous PTH secretion and test the response of the kidney to it. Neither phosphorus nor cyclic AMP increased in urine despite a definite hypocalcemia (6.2 mg/dl) which probably stimulated endogenous PTH secretion (Fig. 2).

Treatment with oral administration of 0.5 μ g/day of 1 α OH-vitamin D₃ for 40 days failed to raise serum Ca but an increase of the dose to 2 μ g/day resulted in a rise of serum Ca to the normal level after 3 days. Serum total protein and albumin were unchanged throughout this period. No side effects such as nausea, indigestion and skin eruptions were found. Paresthesia also disappeared. After 2 weeks, 150,000 units of vitamin D₂ was started to replace 1 α OH vitamin D₃ and clinical symptoms and biochemical abnormalities persistently stayed under control (Fig. 3).

Discussion

The diagnosis of pseudohypoparathyroidism in this case is based on chronic tetany with persistent hypocalcemia, the characteristic physical signs of round face, short stature, short metacarpals and metatarsals, subcutaneous calcification, absence of increase of phosphate and cyclic AMP in urine in response to exogenous PTH and slightly elevated PTH in serum in the absence of renal insufficiency or malabsorption syndrome, and this case apparently belongs to classical Type I (Drezner *et al.*, 1973; Rodriguez *et al.*, 1974). Although serum Ca was definitely low in the past, only a mild hypocalcemia was seen recently with disappearance of tetany and convulsion,

Fig. 2. The Effect of EDTA Infusion on Ca and P Metabolism. Na₂-EDTA, 70 mg/kg body weight dissolved in 200 ml 5% glucose solution, was infused intravenously over a period of 20 min. Both in the patient (solid line) and the normal control (dotted line), serum Ca (closed square) and serum P (closed circle) decreased. Up/Ucr increased markedly in the control (column in dotted line) but not at all in the patient (column in solid line). Urinary cyclic AMP (UCAMP) also behaved similarly.

possibly representing a transitional form between pseudo- and pseudopseudo-hypoparathyroidism.

The treatment of pseudohypoparathyroidism so far consisted of calcium, vitamin D₂ and dihydrotachysterol. Due to a defect in the intestinal calcium absorption, calcium salts even at a high dose level failed to normalize serum Ca and a very large dose of vitamin D was required to obtain a clinical improvement. This might be due to the defect in the kidney of patients with pseudohypoparathyroidism to convert vitamin D into the active form through 1 α OH-hydroxylation (Sinha *et al.*, 1975 and 1976). It thus appears reasonable to use 1 α OH-vitamin D₃ in the treatment of pseudohypoparathyroidism. Kooh *et al.* (1975) used a small dose of 1 α OH-vitamin D₃ (0.04–0.08 μ g/kg), which was found to be quite effective in pseudohypoparathyroidism, while 3–5 μ g of 25-OH-vitamin D₃ was required to obtain similar effect. The effective dose of 1 α OH-vitamin D₃ in the present case was

0.03 μ g/kg of actual body weight and 0.04 μ g of ideal body weight, even lower than the dose of 1,25(OH)₂ vitamin D₃, the final active form of vitamin D₃. Neer *et al.* (1975) also reported a favorable effect of 1 α OH- and 1,25(OH)₂ vitamin D₃ to maintain the level of serum Ca in postoperative and idiopathic hypoparathyroidism. These authors demonstrated an increase of urinary calcium and phosphorus excretion without significant changes of renal calcium clearance or urinary hydroxyproline excretion, suggesting an advantage of 1 α OH form of vitamin D derivative in some patients with hypoparathyroidism.

In Japan, 44 cases of pseudohypoparathyroidism have been reported, since the first report by Kudo in 1954, as summarized in Table 1. Males and females were almost equally affected, and the age of onset was below 10 years in 21 (51%), between 11 and 20 years in 12 (29%), 21–30 years in 6 (15%) and above 30 years in 2 (5%). Serum Ca was low in 33 of 35 and serum P high in

Fig. 3. Course of Treatment with 1 α OH-vitamin D₃ and vitamin D. Serum Ca (closed square connected with solid line) rose slightly during administration of 0.5 μ g/day 1 α OH-vitamin D₃ and reached the lower limit of normal 3 days after the beginning of administration of 2 μ g/day and stayed at this level thereafter. Serum alkaline phosphatase shown by open circles connected with solid line gradually fell. Serum P shown by closed circles connected with solid line was almost unchanged. Serum immunoreactive PTH shown by closed circles connected with dotted line showed mild unexplained fluctuations.

31 of 33 cases studied, with borderline values in the remaining cases. Tetany was seen in 32 of 42 (76%) and generalized convulsion in 30 of 40 cases. Short stature was seen in 26 of 34 (77%), round face in 33 of 37 (89%), short metacarpals in 24 of 36 (62%) and soft tissue calcification in 15 of 30 cases (50%).

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Table 1. Cases of Pseudohypoparathyroidism in Japan

No.	Reporter	Year of Report	Age	Sex	Serum Ca mg/dl	Serum P mg/dl	Round Face	Short Stature	Brachy-metacarpia
1	Kudo	1954	24	M	5.6	4.2	—	—	—
2	Torikai	1961	15	M	6.4-7.8	6.9- 8.7	+	+	—
3	Takamura	1964	13	M	5.0	11.0	+	+	+
4	Nakajima	1965	13	M	7.2	6.5	+	+	+
5	Ito	1965	33	F	low	high	+	+	+
6	Matsuoka	1966	27	F	6.6-7.6	8.4-11.4	—	—	—
7	Kuroiwa	1966	19	F	7.8-9.0	8.4-12.0	+	+	+
8	Mizuta	1967	24	F	8.8-9.0		+	+	+
9	Kusakab	1968	32	M	7.8-8.2	5.1- 5.4	+	+	+
10	Hirata	1968	24	F	8.8		+	+	+
11	Yano	1968	61	F			+	+	+
12	Usa	1968	35	F	5.6	5.1	+	+	—
13	Awano	1968					+	+	—
14	Miura	1969	23	F	5.4	7.8	+	+	+
15	Okano	1970	22	M	7.9	5.8	+	+	+
16	Tsuchiya	1971	12	F	4.6	8.5	+	—	—
17	Inoue	1971	21	M	5.8-7.5	5.7- 7.2	+	+	+
18	Tayama	1972	13	F	3.2	7.6	+	+	+
19	Miyamoto	1972	27	F	6.2	5.6	+	+	+
20	Maru	1972	8	F	7.2	10.7	+	—	—
21	Iwata	1972	41	M	5.8	5.0	+	—	—
22	Iseki	1973	7	F	6.2	9.7	+	+	—
23	Tanimura	1973	12	M	4.6-5.6	6.1-10.0	+	—	+
24	Shinkawa	1973	11	M	6.2	7.2	+	+	+
25	Oguchi	1973	17	F	5.0	7.0	+	+	+
26	Kawano	1973	13	M	5.6	8.6	+	+	
27	Saito	1973	28	M					
28	Saito	1973	25	F					
29	Iizuka	1973	3				+	—	+
30	Uchimura	1973	40	F	7.2	4.1	+	+	+
31	Minemawari	1974	31	F	4.5	6.2	+	+	+
32	Yoshikawa	1974	12	M	3.8-6.8	6.8- 7.2	+	+	—
33	Watanabe	1974		M	6.4	4.7			
34	Kodama	1974	2M	M	4.6	5.8	—	—	—
35	Yakura	1974	27	F	6.0	6.0	+	+	+
36	Sumiyoshi	1974	8	F					
37	Ishimaru	1975	14	M	6.7	9.2	+		+
38	Soeda	1975	35	F	7.6	5.2	+	—	+
39	Morishita	1975	8M	M	6.6	9.5			—
40	Mochizuki	1975	21	M			—	—	+
41	Bessho	1975	6	M					
42	Bessho	1975	3	M					
43	Matsuya	1975	22	M	6.0	7.0	+	+	+
44	This Case	1976	37	F	5.2-6.6	4.5	+	+	+

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