1967

Review of idiopathic hypoparathyroidism

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REVIEW OF

IDIOPATHIC HYPOPARATHYROIDISM

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Submitted in Partial Fulfillment
for the Degree of Doctor of Medicine

COLLEGE OF MEDICINE, UNIVERSITY OF NEBRASKA

February 1, 1967

OMAHA, NEBRASKA

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INTRODUCTION

The parathyroid glands function to control the balance between extracellular calcium and phosphate. This is done by the production of a hormone called parathormone, which is the only product of these glands to present knowledge. They control the body reserve of calcium which resides in the bones, withdrawing it when serum calcium is low, probably by stimulating osteoclastic activity in the bones and acting on the kidney tubular epithelium to promote the excretion of phosphate, thereby forcing a shift to maintain the serum solubility product existing between Ca:P (43).

The exact mechanism of action of parathormone is not well understood and has, for several years, been under some controversy in the literature. There has been experimental evidence that shows parathormone can control calcium concentrations in extracellular fluid, regardless of the concentration of phosphate and regardless of whether the kidneys are present in the body (18). In addition to this, it has been shown that concentration of phosphate in the blood or urine does not always change predictably when exogenous parathormone is administered. Serum calcium levels however do change predictably, thus predisposing to the idea that parathormone has direct action on osteoclastic activity and/or bone demineralization and no relationship, or, an inconstant one toward phosphate level as controlled by the renal tubules (2).

If the parathyroids do not secrete sufficient hormone, bone resorbtion is depressed so that the level of extracellular calcium decreases. When calcium levels fall below 10 mg.%, a general neuromuscular irritability may be seen. When the calcium level falls to about 7 mg.%, the classic signs of tetany develop. This could result in death, especially if the sensitive muscles of the larynx are caused to go into spasm, with obstruction of respiration.

Historically, the most prevalent cause of hypoparathyroidism has been the removal of parathyroid tissue incident to surgical intervention for thyroid hyperfunction. Each of the four parathyroid glands measures only 6x3x2 mm. and each has the gross appearance of dark brown fat. Normally they are located one each behind the four poles of the thyroid, but there may be fewer or more than four glands and they may be located in the anterior or posterior mediastinum. It is easily seen why the parathyroid glands were removed with thyroidectomy by generations of surgeons (21).

HISTORICAL

Drake, Albright, Bauer, and Castleman (8) set forth in 1939 criteria for the diagnosis of idiopathic hypoparathyroidism in the absence of a history of thyroid gland surgery. These criteria are: 1. a low serum calcium level; 2. a high serum inorganic phosphorus level; 3. absence of roentgenologic signs of rickets and osteomalacia; 4. chronic tetany; 5. absence of renal insufficiency, steatorrhea, chronic diarrhea, and alkalosis. A sixth criterion,

consisting of an acute phosphate diuresis following the intravenous administration of potent parathyroid extract or a therapeutic response to adequate intramuscular administration has been suggested by Strom and Winberg (36) as a differentiating point from pseudohypoparathyroidism. Steinberg and Waldron (35) in analyzing 52 cases of idiopathic hypoparathyroidism selected their cases only from the criteria established by Drake and associates. They did not require a response to parathormone as a criterion for the diagnosis. Other authors have also rejected the additional sixth criterion in establishing the diagnosis of idiopathic hypoparathyroidism as compared to pseudohypoparathyroidism (23,44). This, at least in the author's mind, left some doubt as to exactly what criterion needed to be met to establish a diagnosis of idiopathic hypoparathyroidism, and created some confusion when comparing data of separate authors for analysis before 1957.

Bronsky, Kushner, Dubin, and Snapper (4) 1957, in an attempt to clarify the situation, selected cases that satisfied at least four of the five criteria of Drake, eliminating all those with steatorrhea, osteomalacia and renal insufficiency. In addition these patients had the good response to parathyroid extract, either acutely or therapeutically or a finding of the absence of parathyroid glands at autopsy. The Ellsworth Howard test (11) was accepted as a means of determining the acute renal response to parathyroid extract. A good response to this test indicated an increment in the hourly excretion of phosphate exceeding control

levels by either 40 mg.% or 250 mg.%.

ETIOLOGY

As the name implies, ~~this for~~ the etiology of hypoparathyroidism is "idiopathic" and the exact cause or causes are not known. Drake and associates (8) suggested that the cause for idiopathic hypoparathyroidism was due either to destruction of all parathyroid tissue by infection or post-natal hemorrhage, or to congenital aplasia of the glands. Absence or replacement of parathyroid tissue in idiopathic hypoparathyroidism has been demonstrated at autopsy in 8 instances, to my knowledge. Stutphin and co-workers (37), Hayman and Marcus (21), both noted the frequent association of moniliasis with idiopathic hypoparathyroidism and postulated a possible etiologic role. Bruce and Strong (5) and Ludwig (29) have attributed the state of idiopathic hypoparathyroidism to maternal hyperthyroidism. In Ludwig's review of the literature, all of the hypoparathyroid tetany that developed in the new born infants was transient and in only one case was the hypoparathyroidism permanent.

In summary then idiopathic hypoparathyroidism presumably results from the following: 1. congenital aplasia of the parathyroid glands; 2. loss of some trophic hormone (unlikely since the parathyroid glands are not known to be dependent upon any trophic hormone); 3. presence of some circulating toxin with an affinity for parathyroid tissue; 4. predilection of the parathyroid glands for some infection which might cause atrophy and destruction of all

the glands.

CLINICAL FEATURES

Idiopathic hypoparathyroidism is a rare disease. Kawalski (23) in 1941 found only eleven cases in the records of Mayo Clinic. Buckwalter and associates (6) noted between 1927 and 1955 only one case of idiopathic hypoparathyroidism had been observed at the University of Iowa Hospitals. Wise and Hart (44) reported two cases of idiopathic hypoparathyroidism from 620,000 admission in a ten year period to King's County Hospital. Only two cases were observed among 434,768 admissions to Cook County Hospital in the five years between 1953 and 1957.

Sex and age distribution: In idiopathic hypoparathyroidism sex distribution is equal. According to Bronsky and associates (4) in their series of 50 patients, the average age of onset is 17 years of age, with 58% starting from birth to ten years of age, 12% from eleven to twenty years of age, 4% from twenty-one to thirty years of age, 16% from thirty-one to forty years of age, 8% from forty-one to fifty years of age, and 2% above fifty years of age. The duration of symptoms prior to establishment of the diagnosis averaged from nine to twelve years. Individual cases have been reported which, though symptomatic, remained undiagnosed for 30 and 40 years (35,22). In other instances, the diagnosis was suspected at birth (38) or established within weeks of the onset (31). The stated ages for the onset are probably too great, for

the onset is determined by the time of appearance of the first symptoms clearly due to tetany. Hypoparathyroidism may apparently exist for many years prior to the appearance of overt symptoms. For example, Bronsky and associates reported a case in which tetany appeared at the age of 16 years, yet x-ray revealed arrest of dental maturation at about 10 years of age.

Symptoms: The most striking clinical manifestation observed is convulsions, which appear in approximately two-thirds of all reported cases. They resemble, in general, grand mal seizures of idiopathic epilepsy, but the preceeding aura, loss of consciousness, involuntary trauma or sphincter incontinence is often absent. Rarely, the seizures may resemble the petit mal varient of epilepsy (3,27). The electroencephalogram is also frequently abnormal making the correct diagnosis even more difficult (17). As a result of this many patients are falsely diagnosed as having epilepsy. Of diagnostic significance however, antiepileptic therapy is invariably ineffective, signs or symptoms of tetany almost always preceed the appearance of seizures, anti-tetanic therapy usually secures relief from seizures and that coincident with restoration of a normal serum calcium level, abnormal electroencephalograms become normal (16). Idiopathic epilepsy and tetanic convulsions are, therefore, distinct entities.

The manifestations of hypoparathyroidism follow no predictable course. The presenting symptoms may be all or any of those mentioned above. Tetany, particularly tetanic convulsions, may be

manifest infrequently occupying a short period of the patients untreated course or may occur so often as to seriously incapacitate the patient (14). Although still unexplained, even in untreated patients, long periods of complete remissions from symptoms may occur. Certain factors are reported to be capable of precipitating tetany. These include exercise, excitement, and emotional upheavals. It has been reported that even trivial exertion may provoke painful spasms that render the patient bed fast (35). Harvey and Liliethal (20) demonstrated that intraarterial epinephrine evokes tetany in hypocalcemic patients. This probably represents the mechanism of tetany production with physical exertion and emotional disturbances. There is a striking tendency for tetany to appear during menstruation (14). The onset of idiopathic hypoparathyroidism in children is often associated with an infectious disease.

The gastrointestinal disturbances of vomiting and constipation are observed frequently in idiopathic hypoparathyroidism. Congestive heart failure has also been seen in idiopathic hypoparathyroidism. In a twelve year old girl reported by Schulman and Ratner (33), congestive failure improved with treatment of tetany.

Mental changes are observed frequently in idiopathic hypoparathyroidism. Irritability, emotional lability, moroseness, impairment of memory, and mental confusion are often described. The patient developing tetany in adult life may show a loss of pride in personal appearance and intellectual deterioration (4). Steinberg and Waldron (35) commented on an odd irrational screaming

which may develop in some of these patients. Frank depressive psychosis has been reported by Emmerson, Walsh, and Howard (12) and again by Robinson, Kallberg, and Crowley (32) which differs from that observed due to thyroid surgery.

Hereditary Factors: There is only slim evidence for hereditary factors being responsible for idiopathic hypoparathyroidism. Stutphin, Albright, and McCune (37) however reported on five cases of idiopathic hypoparathyroidism associated with moniliasis in which three of the cases were siblings. Goldman and associates (15) reported two siblings with idiopathic hypoparathyroidism. Ludwig (29) in reviewing the literature found only one infant being born of a patient with hyperparathyroidism in which the symptoms of hypoparathyroidism persisted indefinately.

Signs: Adequate physical description of patients with idiopathic hypoparathyroidism, from the literature, is far from complete, but it is notable that they have been described by Bronsky and associates (4) as tall, thin, and slender. Four of their patients, two over, and two under seventeen years of age were about 60 inches tall (average 63 inches). Actually people with idiopathic hypoparathyroidism have a body habitus which conforms quite closely to the general population.

The most common ocular finding is cataracts, and the most unusual is papilledema. Cataracts were present in fifty per cent of the reported cases of idiopathic hypoparathyroidism by Bronsky and associates (4). Characteristically, they are bilateral and

lameilar in type involving the subcapsular areas of the cortical portion of the lens. The central nuclear portion of the lens is usually spared early in the disease but in time complete opasification may occur (1). The time from onset of the disease to the appearance of cataracts is extremely variable. Papilledema has been reported in nine patients with idiopathic hypoparathyroidism. This sign is accompanied frequently by elevation of the cerebrospinal fluid pressure, convulsions, and sometimes unilateral neurological manifestations, simulating a cerebral tumor (37).

Dental defects are very common in cases of idiopathic hypoparathyroidism, but the type of dental defect is a result of the age of the patient at the time of onset of the disease. Defective enamel and root formation, dental hypoplasia, and failure of adult teeth to erupt are the anomalies usually found (2). These people usually become edentulous at an early age as compared to the general population.

Ectodermal changes are fairly common in idiopathic hypoparathyroidism. The skin is often found to be dry, puffy, and coarse (34). The scalp is often found to be dry, and the hair coarse, brittle, sparce, and lacking in lustre. Emmerson, Walsh, and Howard (12) reported that patchy alopecia is occasionally observed with the eyebrows, eyelashes, axillary and pubic hair quite scanty. The nails, when involved, are thin, brittle, deformed, and tend to split at the free edge. Most characteristic is the presence of transverse grooves (34).

Monilial infections of the nails and mouth have been observed with idiopathic hypoparathyroidism, and cultures from the nails and the pharynx frequently grow candida albicans. The infection is resistant to therapy even after the serum calcium has been brought up to normal. Nail changes of moniliasis and hypoparathyroidism are different, but frequently they coexist (21). In moniliasis, the nails are irregularly affected, are pitted, appear flaky, and are unaffected by therapy for hypoparathyroidism. In hypoparathyroidism alone, all the nails are involved, smooth, but transversely grooved and become normal after the serum calcium level becomes normal (37).

Mental retardation, normal, and even superior intelligence may be found in patients with idiopathic hypoparathyroidism. Bronsky and associates (4) found from their literature review, 11 patients with normal intelligence and 9 patients with subnormal intelligence. In general, mental retardation seems to be greater the earlier the onset of the disease and the longer treatment is delayed because of the inability to make the diagnosis.

The neurologic examination in idiopathic hypoparathyroidism is usually unremarkable, but sometimes may disclose some unexpected findings such as pseudo-tumor cerebri previously mentioned. One may find examples of reported cases with areflexia and instances where hyperreflexia have been found. The superficial reflexes are always intact and pathologic reflexes have not been reported (4). Steinberg and Waldron (35) reported finding transient hemiparesis

occuring as the result of a convulsion. Signs suggestive of Parkinsonism and indicative of an extrapyramidal tract lesion have been described by many authors (4). These signs are loss of facial expression, a tilted, only rarely propulsive gait with arms held stiffly at the sides, and a pill rolling tremor. Basal ganglia calcifications occur in some, but not all of these reported cases. The signs of latent tetany such as Chvostek and Trousseau signs are observed with great frequency. In general the Chvostek sign is almost always present. For the Trousseau sign to be present in its absence or for both signs to be absent is very unusual (4).

The tendency toward deposition of calcium in the lens, brain, and subcutaneous tissues is a function of hypocalcemia. The lenticular opacities have already been discussed. Intracranial calcifications occur frequently in both syndromes. They are usually manifest on x-ray as symmetrical punctate depositions localized in the basal ganglia. Less often, symmetrical calcifications of the choroid, cerebellum, or cerebrum are observed, but these usually coexist with basal ganglia calcifications. Pathological descriptions of this lesion are wanting, but are probably similar to those observed in postoperative hypoparathyroidism, that is, dystrophic depositions of calcium granules in the interstitial capillaries, media, and adventitia of the small and medium sized arterioles of the basal ganglia (40). Subcutaneous calcifications have been reported only once in idiopathic hypoparathyroidism. Slight tendon and intramuscular calcifications have been noticed only twice.

Abnormalities of skeletal calcification resulting in either increased or decreased bone density are present in idiopathic hypoparathyroidism. These changes are very difficult to assess radiologically and even more difficult to interpret from written descriptions. Increased bone density is most frequently present in idiopathic hypoparathyroidism. Changes localized to individual bones, while reported often are difficult to evaluate for although in some reports a comparison is made to other bones, in others there is no evidence that the entire skeleton was examined radiologically (4). An increased bone density would be expected in hypoparathyroidism as contrasted to the findings in hyperthyroidism, although actually the bone density is usually normal. Decreased skeletal density is therefore an unexpected finding. In these instances, decreased intestinal absorption of calcium may overshadow a decrease in osteoclastic activity. The former will tend to decrease and the latter to increase skeletal calcification. The alkaline phosphatase levels when reported in these cases were normal.

Laboratory Values: The reported serum calcium levels are rarely above 7.5 mg.% and the serum inorganic phosphorus levels are seldom less than 5.0 mg.% in adults or 7.0 mg.% in children. The urinary Sulkowitch test is usually negative, but may be positive despite a low serum calcium level and absence of demonstrable renal abnormalities (36). The 24 hour excretion of urinary calcium as reported in a few cases ranged from 4 to 75 mg. Uric acid levels are seldom determined in this disease, but Dubin and

associates (9) indicate that hyperuricemia is a frequent finding in hypoparathyroidism.

The cerebrospinal fluid was examined in 12 cases of idiopathic hypoparathyroidism. The only abnormality observed was elevated pressure in four cases, all had papilledema. In four other cases, papilledema was associated with normal spinal fluid pressures. Elevated spinal fluid pressures were observed to return to normal levels after successful antitetanic therapy (4). The electroencephalogram in idiopathic hypoparathyroidism is usually abnormal. The most characteristic abnormality is abnormal presence of slow waves, 2 to 5 per second, occuring either singly or in series, with occasional interspersed spikes (17). These are enhanced by hyperventilation. Paroxysmal discharges, sometimes localized, may be noted with seizures. Following successful antitetanic therapy, the electroencephalogram shows marked improvement or more usually becomes normal (17).

The electrocardiogram in idiopathic hypoparathyroidism is usually within normal limits except for prolongation of the Q-T interval. This characteristic abnormality has sometimes been the first clue to the correct diagnosis. With restoration of a normal serum calcium level, the Q-T interval returns to normal. T-wave abnormalities are observed frequently. Inversion of the T-waves with reversion to the upright position after therapy has been reported (4).

Associated Diseases: Addison's disease has been reported in

five patients with idiopathic hypoparathyroidism (13,25,36,40). As a general rule, the hypoparathyroidism preceeds the adrenal insufficiency by several years, and in the case reported by Whitaker and associates (41), moniliasis was present prior to both diseases. Autopsy report on one of these reported cases revealed adrenal cortical atrophy associated with the absence of parathyroid glands. The relationship of these diseases to one another and the effect of steroid therapy to serum calcium has not been well worked out to the present. There has been little success in identifying other endocrine abnormalities in hypoparathyroidism. B.M.R. and serum cholesterol are usually normal. Glucose tolerance tests have resulted in variable responses. The sexual development is normal and these patients may have children.

Reisner and Ellsworth (30) report one case of pernicious anemia in idiopathic hypoparathyroidism. This disease is very rare in people less than 20 years of age and therefore deserves mention. Thalassemia minor has been reported in two siblings with idiopathic hypoparathyroidism (37).

Prognosis: The duration of life is good even in patients who are not treated. In two patients with idiopathic hypoparathyroidism who have died, their death may have been related to the treatment of the disease (4). One patient died of a hemorrhagic diathesis after maintenance on increasing larger doses of parathyroid extract for six years (7). The other died after a toxic reaction to sodium ethylene diamine tetra-acetate used to treat hypercalcemia induced

by vitamin D therapy (10). Drake and associates (8) report that one of their patients died of septicemia. Four patients died of Addison's disease (13,25,28,41). The development of Addison's disease during the course of idiopathic hypoparathyroidism carries with it a grave prognosis. The type of death one would expect, that of tetany, asphyxia from laryngospasm or trauma due to convulsions, has not been observed as yet. Patients with untreated hypoparathyroidism of unknown etiology suffer from a high morbidity, with recurrent convulsions, painful muscular spasms, cataract formation, and mental changes. All of these manifestations may seriously impair the patient's performance in life.

Pathology: Autopsies have been reported in eight cases of idiopathic hypoparathyroidism. In one case, parathyroid glands were identified on gross inspection, but microscopic examination revealed complete replacement of parathyroid tissue by fat (8). In a report by Treusch and Cohen (39), only one small atrophic parathyroid gland 0.1 cm. in diameter was found. This gland showed increased fibrosis, definite cellular atrophy, and nuclear pyknosis as compared to a normal gland. In the others, absence of parathyroid tissue was demonstrated by adequate search of the neck, thyroid gland, and mediastinum. In four cases, atrophy of the adrenal cortex was an associated finding. The renal and osseous structures when described were normal.

Therapy: The treatment of acute tetany consists of slow intravenous administration of calcium gluconate until the symptoms have

been controlled.

Long range therapy of hypoparathyroidism can be effectively achieved by dihydrotachysterol (A.T.-10 or Hytakerol). The principle action of A.T.-10 is that of phosphate diuresis. At the same time, the absorption of calcium from the gut is markedly enhanced. The recommended dosage is 3 cc. (1.25 mg.) daily. Calcium intake should be increased by administering calcium lactate or gluconate. Milk must not be used as a source of calcium because of its high phosphorus/calcium ratio. Simultaneously, an aluminum hydroxide gel may be taken to diminish the intestinal absorption of phosphate. Attempts may be made to produce mild acidosis, therby increasing the ionized portion of the serum calcium and further decreasing the likelyhood of tetany.

The most common method of treatment is administration of vitamin D. This vitamin is even more active than A.T.-10 in increasing intestinal absorption of calcium and is just about as effective in increasing renal excretion of phosphate. Large doses of vitamin D are given daily until serum calcium levels reach 10 mg.%. Thereafter, a maintenance dose of 50,000 to 200,000 I.U. is administered daily. It is the prevailing opinion that most patients, especially those with postoperative hypoparathyroidism can be well maintained on daily doses of 10,000 or 20,000 I.U. There have been several observations of hypercalcemic coma caused by over dosage of vitamin D in such instances.

Rarely the oral administration of vitamin D does not produce

satisfactory results and parenteral administration is necessary. Injection of parathyroid extract can also be used to control hypoparathyroidism. However, this preparation is expensive and antibodies may develop, rendering it ineffective.

During treatment the urinary phosphorus increases as the fecal phosphorus decreases. Then fecal calcium decreases as the serum calcium rises to normal levels.

The clinical results of treatment with these preparations are usually good. Nevertheless, we must remember the treatment is purely symptomatic. Attempts to transplant parathyroid tissue have been unsuccessful (42).

SUMMARY AND CONCLUSIONS

The attempt has been made in this paper to review the literature on idiopathic hypoparathyroidism, summarizing and synthesizing the information obtained into useful form. The term idiopathic hypoparathryroidism in this paper refers to those patients who fill the criteria of Drake and associates (8), and in addition, have a specifically good response to the administration of parathormone. This differentiates the group designated by Albright (2) as pseudohypoparathyroidism.

Factors which generally characterize these patients have been commented on. In idiopathic hypoparathyroidism there is an equal sex distribution. The average age of onset is 17 years of age, but generally the age of onset may be any age up and through the fifth

decade of life. Familial hypoparathyroidism was found, by my research to be quite uncommon. These patients tend to be short of stature, but some have been found to be above average height. Face and body build are essentially normal. Papilledema has been found infrequently with and without increased central nervous system pressure. Skeletal deformities are uncommon. Moniliasis and Addison's disease are the two most frequent accompanying diseases. Addison's disease being a bad prognostic sign. At autopsy, the parathyroid glands are either absent or replaced with fat or fibrosis.

Treatment of acute tetany consists of intravenous administration of calcium gluconate. Long range therapy can be achieved by the use of Dihydrotachysterol or vitamin D and increased calcium intake. Parathormone has no place in long range treatment of hypoparathyroidism.

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