Shingles (Varicella Zoster) Outbreaks in Patients with Hyperparathyroidism and Their Relationship to Hypercalcemia

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Shingles (varicella zoster) can be a presenting symptom of hyperparathyroidism and occurs twice as often (rate, 3.7%) among patients with hypercalcemia than in age-matched cohorts of patients >40 years of age who have normal calcium levels. The incidence of shingles increased in a linear fashion, from an annual rate of 1.5% among patients with serum calcium levels <10.5 mg/dL to 11% among patients whose calcium levels reached 13 mg/dL (P<.05), a rate that is 6 times greater than that among age-matched historical control individuals (P<.05).

Primary hyperparathyroidism (PHPT) is typically associated with hypercalcemia of various degrees. The elevated calcium levels are believed to have a direct effect on central and peripheral nerves, affecting evoked potentials and nerve conduction [1, 2]. It is widely held that the effect of calcium on the nervous system is the origin of the classic neuropsychiatric symptoms that are often seen in patients with PHPT [3], although these symptoms do not necessarily increase in intensity or frequency as calcium levels increase.

Shingles is the cutaneous manifestation of the reactivation of varicella-zoster virus, which leads to a group of painful blisters over a specific neurologic dermatome. The virus can lie dormant for decades in the dorsal root ganglion until it is stimulated to reactivate and reproduce down the path of the nerve to the surface of the skin. The stimulation for viral reactivation is quite variable and includes stress, immunocompromised states, severe illness, and use of corticosteroids [4–6].

The association between shingles and PHPT has been reported previously in a patient with hypercalcemic crisis [7]. However, there is little known about this association and whether high calcium levels play a role in inducing viral outbreaks. Our experience in treating several thousand patients with PHPT per year exposed what we believed to be a higher-than-usual incidence of shingles among these patients, which prompted this prospective study. Because of the predilection of shingles to occur in patients >40 years of age, our study was confined to patients in this age group.

Methods. During an 8-month period ending September 2007, 1162 patients underwent surgery for PHPT at a single medical practice treating parathyroid disease exclusively. Of these 1162 patients, 1000 were aged 45–80 years (the age range with the highest incidence of shingles in the United States); these patients comprised the study group. Patients were questioned regarding an outbreak of shingles, during the 12 months preceding surgery, for which they sought medical attention and that was therefore documented in their medical records. To be included, the patient had to see a physician who made the diagnosis of shingles by observation of dermatome-limited lesions while noting the appropriate clinical presentation.

Data on clinical signs and subjective symptoms typically associated with PHPT were obtained from all patients via a computerized questionnaire, as described by our group and others elsewhere [8], and comparisons were made between patients with and patients without shingles. Biochemical parameters—including serum calcium, urinary calcium, and serum parathyroid hormone (PTH) levels—were analyzed for differences between patients with and patients without shingles.

All patients were established to have PHPT by assessment of biochemical and clinical parameters and underwent curative parathyroidectomy [9]. All operations were conducted at least 3 weeks after resolution of the viral outbreak. Proof of biochemical cure of hyperparathyroidism after surgery was a requirement for inclusion in this study. All data were collected in a secure database without patient name recognition, in compliance with all National Institutes of Health guidelines and as approved by our local scientific and ethics advisory board.

All results are expressed as mean ± SD. Quantitative values were compared using the t test for unpaired values. Variables that were not normally distributed were expressed as median values and were assessed by use of the Mann-Whitney rank sum test for nonparametric data. Correlations between variables have been evaluated by simple or multiple regression analysis (as appropriate). P<.05 was considered to be significant. Data from meta-analyses published elsewhere [10, 11] were used for

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comparisons between shingles incidence among patients with PHPT and shingles incidence among patients >45 years of age without PHPT in the US population. Data were analyzed by use of the Sigma Stat Program (SPSS).

**Results.** Thirty-seven (3.7%) of 1000 patients aged 45–80 years had a documented case of shingles in the 12 months before surgery (table 1). Eight patients (22%) had ≥1 previous episode within the past 5 years, all associated with high serum calcium levels. The average age of patients with PHPT and shingles was 63.1 ± 8.9 years (range, 47–78 years). The study group contained 752 women (75.2%) and 248 men (24.8%) who did not have shingles, and the group with shingles contained 29 women (78.4%) and 8 men (21.6%) (P = .82). Twenty-two patients (82%) had known PHPT at the time shingles appeared, whereas 5 (18%) had PHPT diagnosed while they were seeking medical care for shingles. Shingles occurred in patients with calcium levels ranging from 10.2 to 13.8 mg/dL but was significantly more common among patients with calcium levels >12 mg/dL (P < .05) (figure 1). The peak incidence occurred among patients with serum calcium levels ≥13 mg/dL, with 11% of these patients having an episode of shingles in the preceding 12 months. This rate is 5.8 times the highest expected incidence of shingles in the US population of this age group (P < .01).

There was no difference in preoperative PTH or urine calcium levels between patients with and patients without shingles. The number of associated self-reported symptoms was similar between patients with and patients without shingles (5.1 ± 2.2 vs. 5.4 ± 2.4, respectively; P = .71). However, the types of symptoms reported differed, in that patients with shingles were more likely than patients without shingles to claim that they had baseline peripheral neurologic symptoms, such as neuromuscular weakness/cramps (before the shingles outbreak) (17.7% vs. 29.6% for control individuals vs. patients with shingles, respectively; P < .05). At the time of surgery, all patients with shingles had a parathyroid adenoma as the cause of their hyperparathyroidism.

**Discussion.** Shingles can arise only in individuals who have been previously exposed to chickenpox (varicella). After an attack of chickenpox, the varicella-zoster virus typically retreats to nerve cells within the dorsal ganglion of the spinal cord, where it can lie dormant for several months to several decades [4–6]. The emergence of the virus as a cutaneous disease occurs after various events that depress the immune system, such as aging, severe emotional stress, severe illness, immunosuppression, or long-term use of corticosteroids. In some cases, there is no inciting event identified. The cellular and immunological events that lead to reactivation remain poorly understood.

Before implementation of the universal varicella vaccination program in the United States, ~95% of the US population developed chickenpox before 18 years of age. As these patients aged, their incidence of shingles increased in association with a presumed progressive decline in immunity to varicella-zoster virus [6]. Since 1995, >60% of American children have been vaccinated against chickenpox, and the number of shingles outbreaks is significantly lower among younger patients than it has been in years past. The incidence of shingles is highest among persons who are >60 years of age, with an incidence rate of ~12–19 cases/1000 individuals/year in the United States, depending on the methodology of the study [10–12].

The present study suggests that the hypercalcemia associated with PHPT can induce varicella-zoster virus to emerge from dormancy, presenting as shingles. The rate at which patients with normocalcemic PHPT develop shingles (1.5% per year) is no different than the expected occurrence in the general population >50 years of age (1.2%–1.9% per year). However,
as serum calcium levels increase, so does the incidence of shingles, reaching a peak annual incidence of 6.8% among patients >45 years of age with calcium levels >12.0 mg/dL and as high as 11% among patients with calcium levels >13 mg/dL. This is 3–9 times the expected rate in this age group.

Possible causes of the emergence of varicella-zoster virus in patients with PHPT are the “stress” associated with a chronic disease (PHPT), fear of surgery, direct effects of PTH itself, direct effects of calcium on the nerves harboring the virus, and direct effects of elevated calcium levels on the dormant virus itself. There was no correlation between PTH values and the incidence of shingles; thus, there is no evidence to support this cause. Furthermore, direct effects of PTH on nervous tissues have not, to our knowledge, been described previously. Similarly, there is no evidence that the stress of chronic PHPT or the stress associated with a patient pondering surgery plays a role. If this were the case, we would expect the occurrence of shingles to be erratic or uniform across all patient groups.

It is an important observation, therefore, that there is a direct correlation between the degree of serum calcium level elevation and the occurrence of shingles. Although hypercalcemia appears to play a central role in this process, it remains unclear whether this is a result of direct effects on the nerve harboring the virus or, possibly, of the awakening of the dormant virus in the presence of high calcium levels. The mechanism by which varicella-zoster virus emerges from latency is not completely understood, but activation of certain calcium channels and their associated calcium fluxes have been implicated [13]. It is interesting that patients who developed shingles were significantly more likely to claim to have baseline peripheral muscular weakness or neuropathy before developing shingles than were their age- and sex-matched cohorts who did not have an outbreak, but we cannot comment on why this would be so. It is also remarkable that 22% of our patients have had >1 episode in the 5 years preceding surgery, yet none of them have any other risk factor known to be associated with viral outbreaks. This rate of recurrent disease is much higher than expected [12].

Shingles can be the presenting symptom of hyperparathyroidism, but, most commonly, it occurs in patients with known parathyroid disease. As calcium levels increase, so too does the incidence of shingles outbreaks, which can recur if the parathyroid disease is not cured. As soon as the outbreak has subsided, curative parathyroid surgery is indicated.

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