Case Report

Treatment of Calcinosi s in Juvenile Dermatomyositis with Probenecid: the Role of Phosphorus Metabolism in the Development of Calcifications

LIORA HAREL, Gideon HAREL, LIORA KORENREICH, RACHEL STRAUSSBERG, and JACOB AMIR

ABSTRACT. Objective. To report the efficacy of probenecid for calcinosis of juvenile dermatomyositis (JDM) and assess the changes in phosphorus metabolism during treatment.

Methods. Biochemical studies of calcium and phosphorus metabolism were performed in a 9-year-old girl with JDM and extensive calcifications before and during probenecid treatment.

Results. The calcifications resolved over 18 months of treatment. Probenecid was found to be effective in reducing calcifications by increasing renal phosphate clearance.

Conclusions. The tendency for calcifications in some patients with JDM might be related to an increase in renal phosphate reclamation, and therefore, probenecid treatment may be effective in these patients. (J Rheumatol 2001;28:1129–32)

Key Indexing Terms: JUvenile DERMATOMYOSITIS CALCINOSiS PROBENECiD

Calcinosis is a devastating complication of juvenile dermatomyositis (JDM) and a difficult therapeutic problem. We report a girl with severe calcinosis of JDM, effectively treated with probenecid and discuss the metabolic aspects of treatment.

CASE REPORT

In November 1994, a 4-year-old girl presented with progressive, painful muscle weakness and rash. She was dysphagic, dysphonic, and unable to walk or sit, with malar rash, heliotrope eruption on eyelids, Gottron papules, periungual erythema, mouth and skin ulcers. Creatine kinase level was 12,000 U/l (normal range 60-149). Electromyography and muscle biopsy confirmed the diagnosis of JDM.

The patient was treated with a 3 day course of IV methylprednisolone 30 mg/kg/day followed by prednisone 2 mg/kg/day. Remarkable improvement was noted in muscle strength and enzymes over 2 months. In March 1995, owing to disease activity while tapering steroids, methotrexate and hydroxychloroquine were added. She had excellent improvement of rash.

In August 1996, due to persistent rashes, methotrexate was replaced with cyclosporin A (10 mg/kg/day). As the muscles and skin disease improved, prednisone was tapered to 10 mg every other day.

The first calcifications were noted in March 1996. Calcium deposits increased rapidly in muscles, tendons, and skin, disseminating along the neck, arms, chest, abdomen, and lower extremities. The calcifications caused severe pain, intermittent fever, recurrent cellulitis, venous congestion of the upper body, and impaired gait.

In January 1998, probenecid was begun at a dose of 25 mg/kg (500 mg/day), and increased to 1250 mg/day. In June 1998, improvement in calcifications was first noted. There was resolution of fever and pain and of visible calcium deposits. In December 1998, the disease relapsed and a 3 day pulse of IV methylprednisolone was given with an increase in daily prednisone dose and addition of methotrexate. Despite the relapse, there was a remarkable decrease in calcifications on physical examination and radiography. In June 1999, skin and muscle disease were in remission, and calcifications were markedly reduced. No side effects of probenecid were encountered. She reported being physically active. Height and weight were in the 15th percentile for her age.

An initial biochemical investigations revealed elevated serum phosphate and uric acid levels, and maximum tubular phosphate reabsorption/glomerular filtration rate (TmP/GFR). Serum levels of parathyroid hormone (PTH) (chemiluminescent enzyme immunoassay, DPC Company, Los Angeles, CA) were normal as were serum calcium, 1,25dihydroxyvitamin D, creatinine, and magnesium before and during probenecid therapy. Following probenecid therapy, serum phosphate, uric acid levels and TmP/GFR decreased and alkaline phosphatase increased.

Biochemical investigations in January 1998 revealed extensive deep and superficial soft tissue calcifications, involving the shoulders, the base of the neck, elbows, and forearms (Figure 1). The chest and abdominal wall had numerous scattered calcifications. Massive calcifications were seen in the lower extremities around hips, shins, knees, and ankles. The bones were osteopenic.

Repeated skeletal survey in July 1999 showed a remarkable reduction in the calcifications, with an improvement in the bone mineral content (Figure 2).

DISCUSSION

Approximately 30-70% of children with JDM develop calcinosi s1,2. Although spontaneous regression of the calcium
deposits may be anticipated, calcinosis may be responsible for longterm disability after remission of myositis. The pathogenesis of calcification in JDM is unknown, though it is thought to develop by release of mitochondrial calcium from damaged muscles into matrix vesicles, which then promotes mineralization. Lesions show calcium hydroxyapatite crystals within disordered collagen fibrils and extracellular tissue matrices. The tendency for calcinosis may be related to the extent of muscle damage; however, reports of severe calcinosi but relatively mild muscle disease may point to other explanations.

Several medications have been used to treat calcinosis but none has been found consistently effective. Corticosteroids and immunosuppressive agents do not stop the development of calcinosis.

Probenecid, a sulfonamide derivative, is a uricosuric
agent that inhibits the reabsorption of uric acid in the proximal tubule. In the 1950s, probenecid was found to increase urine phosphate excretion and lower serum phosphorus in hypoparathyroidism.

Dent and Stamp reported that probenecid was effective in a patient with progressive calcinosis of chronic arthritis. The response was related to the ability of the drug to decrease serum phosphorus while leaving serum calcium levels unchanged. Meyers and Skuterud described an improvement in calcinosis in 2 patients treated with probenecid. Ansell noted an improvement in 3 of 5 patients with extensive calcinosis of JDM treated with probenecid 2 gm/day. Recently, Eddy described a case of severe calcinosis of JDM treated successfully with probenecid 250-1500 mg/day. A thorough biochemical study before treatment revealed elevated serum phosphorus and increased renal tubular reabsorption of phosphate. The effect of the drug was related to its ability to decrease serum phosphorus by increasing renal phosphate excretion.

The role of serum phosphorus levels in the development of calcinosis is demonstrated in the inherited disorder of tumoral calcinosis, with which affected patients have hyperphosphatemia, and increased renal reclamation of phosphate.

The mechanism of action of probenecid in our patient might be related to decrease in serum phosphorus levels due to increase in renal phosphate clearance. The renal threshold phosphate concentration (TmP/GFR), which was supranormal before probenecid treatment, decreased significantly. Serum calcium and renal calcium excretion remained unchanged. The calcium phosphorus product decreased from 56.4 to 35.6 owing to a decrease in serum phosphorus levels. This probably decreased calcium deposition, though it is unclear how this mechanism resulted in resolution of already deposited calcifications.

It is unclear why this patient was hyperphosphatemic and had increased renal phosphate reclamation, as there was no evidence of hypoparathyroidism, no increase in phosphorus load in diet, and renal function was normal during the studies. Serum PTH levels were normal before probenecid but decreased to subnormal values during 18 months of treatment, possibly because the resolution of calcifications increased serum ionic calcium and suppressed PTH secretion.

The effect of probenecid in resolving the calcifications in our case was dramatic, and the probability of spontaneous remission was low, as the calcifications had been progressive before the start of the drug, and the disease relapsed during probenecid treatment. Its effect was associated with an increase in renal phosphate excretion and a decrease in serum phosphorus during treatment. We suggest that the tendency for calcification in JDM might be related to phosphorus metabolism in addition to the inflammatory damage. Therefore, studies of renal phosphate handling in JDM might be of value in assessment and treatment of the calcifications. Treatment with probenecid might be effective in patients with JDM and increased tubular reabsorption of phosphate.

REFERENCES
5. Bowyer SL, Blanc CE, Sullivan DB, Cassidy JT. Childhood dermatomyositis: factors predicting functional outcome and...