Colchicine-induced myoneuropathy in childhood

Abstract  Colchicine is used in the treatment of gouty arthritis, familial Mediterranean fever, amyloidosis, Behcet disease and dermatoses. Myoneuropathy is a rare side-effect reported either with intoxication or in elderly patients with chronic renal insufficiency causing elevated plasma drug levels. We report the first two cases of myoneuropathy in children, both taking appropriate doses of colchicine, and having normal renal function. The myoneuropathic changes were reversible after stopping treatment. The cause of colchicine myoneuropathy is unclear.

Conclusion  In children treated with colchicine, neuromuscular phenomena of unknown aetiology may be related to the drug, even with a lack of intoxication or renal insufficiency.

Key words  Colchicine · Familial Mediterranean fever · Myoneuropathy · Childhood

Abbreviations  

FMF  familial Mediterranean fever

Introduction

Colchicine is a plant alkaloid known to inhibit mitosis in vitro. It is widely used for a variety of diseases, including gouty arthritis, familial Mediterranean fever (FMF), amyloidosis, and other conditions. Its main side-effects are gastro-intestinal and haematopoietic [9]. Myopathy and neuropathy have been rarely reported, mostly in elderly patients with co-existent renal insufficiency and high plasma drug levels [7].

We report the first cases of myoneuropathy in a 5-year-old boy and a 16-year-old girl, who were taking appropriate doses of colchicine and had no evidence of renal impairment.

Case reports

Case 1

The patient was a 5-year-old boy of North African origin, who had been suffering from recurrent attacks of fever and abdominal pain since 6 months of age. At the age of 2.5 years, FMF was diagnosed and treatment with colchicine (1 mg/day) was initiated. The number of attacks significantly decreased and the child continued to grow normally. At the age of 4.5 years, the colchicine dose was raised to 1.5 mg/day due to the increased frequency of fever and abdominal pain attacks (his body weight at that time was 20 kg). The clinical response was excellent but then he began to complain of paresthesias in his palms and legs. Parents denied overdosing. The use of other drugs, nutritional supplements, home remedies or unusual environmental exposure were excluded. No other side-effects of colchicine were noted.

Physical and neurological examination were normal. ESR was 24 mm/h; fibrinogen 405 mg%. Complete blood count and urinalysis were normal. CPK was 100U/L, SGOT 26U/L; SGPT 17U/L.
L and LDH 390U/L (all within the normal range). BUN was 11 mg\% and creatinine 0.6 mg\%. Laboratory tests for heavy metal toxicity were negative.

EMG findings (antidromic sensory potential at a room temperature of 22°C) showed distal sensory latency in the right median nerve of 3.7 ms (normal values up to 3.5 ms) consistent with sensory neuropathy. Other findings included an increased recruitment pattern, reduced amplitude and short duration motor unit potentials in the left tibialis anterior muscle, all consistent with myopathic changes. Brain CT showed no pathological findings.

The colchicine treatment was stopped for a month. During this period of time, the child had multiple febrile episodes but the paresthesias disappeared. Repeat EMG showed normal distal sensory latency of the right median nerve (2.1 ms) and no myopathic changes.

Colchicine was restarted with a lower dose of 1 mg/day, but due to the recurrent fever the dose was raised to 1.25 mg/day. This level was the lowest used to control the FMF attacks, causing less frequent paresthesias.

Case 2

A 16-year-old girl diagnosed as having FMF by the age of 13 and treated with colchicine 1.5 mg/day with a good response, was referred because of numbness of the soles for 1 year. She denied overdosing or taking other drugs.

On neurological examination, muscle strength was normal, but the ankle reflexes were bilaterally absent. Other reflexes were normal and there was no sensory loss or other neurological finding.

Laboratory tests included normal blood count, CPK, SGOT and LDH values. Creatinine was 0.8 mg\%, BUN 12 mg\%, and urinalysis was normal. EMG showed reduced motor nerve conduction velocity of the right and left tibial nerves (34 and 38 m/sec respectively; normal range 40 and above) and increased distal latency of the right tibial nerve (6.3 ms; normal up to 6), all consistent with tibial neuropathy. No myopathic changes were noted. A trial to reduce the colchicine dose to 1 mg/day was helpful (numbness of the soles resolved) but the patient refused to do a repeat EMG and was lost to follow-up.

Discussion

Colchicine is an alkaloid extracted from the plant *Colchicum autumnale* which interferes with microtubule growth and inhibits mitosis [9]. The drug has a few side-effects, among which gastro-intestinal are the most common. Bone marrow depression has been reported primarily in acute intoxication.

Colchicine causes a characteristic myopathy in animals [13]. Myopathy associated with its long-term use in humans has been rarely reported. Vascular myopathy marked by the accumulation of lysosomes is present in muscle biopsies [7]. The first case reported in the literature occurred with a prolonged administration of unusual high doses [6]. The second resulted from acute intoxication [12]. At present, all cases of colchicine myoneuropathy described in the literature, not due to intoxication, occurred in the elderly with elevated plasma drug levels due to chronic renal insufficiency [3–5, 7, 10, 14, 15, 16].

This is easily explained since the drug and its metabolites are partly excreted by the kidneys and may accumulate when correct dose adjustments are not made.

This paper is the first to describe children taking appropriate doses of colchicine, 1–2 mg/day, who had no evidence of renal disorder or amyloidosis. In Israel, many FMF patients are treated with colchicine, including children. To the best of our knowledge, no case report of myoneuropathy in otherwise healthy children taking colchicine has been reported in the English literature. Unfortunately, the serum colchicine level could not be measured.

Peripheral neuropathy may be caused by many chemicals, toxins and drugs such as heavy metals, lead poisons or antimetabolic drugs. Chronic uraemia may also be associated with neuropathy and myopathy. Neither of these causes existed in our patients.

Usually, patients with myoneuropathy associated with colchicine experience subacute proximal weakness, elevated serum CPK levels and mild polyneuropathy manifested by sensory abnormalities, numbness and distal areflexia [7]. Our first patient mainly experienced sensory neuropathy. The myopathy was probably subclinical (no weakness or abnormal CPK), manifested only by EMG. The findings in the second patient were consistent with neuropathy but not with myopathy (neither clinical nor electromyographic changes).

The pathogenesis of colchicine myoneuropathy is not fully understood. It may involve a disruption of a microtubule-dependent cytoskeletal network that interacts with lysosomes [7]. Experimental studies have shown that colchicine binds to tubulin [12], impairs axoplasmic transport in peripheral nerves [11] and damages myofilaments in skeletal muscle [2]. Autopsy findings showed that neuropathy was associated with myelin degeneration [1].

Discontinuation of colchicine is associated with a return of CPK levels to normal, recovery of muscle strength within 4–6 weeks and electrophysiological improvement, [7, 8] as happened in our first case.

We conclude that in children treated with colchicine, neuromuscular phenomena of unknown aetiology may be related to the drug even with a lack of intoxication or renal insufficiency.

References