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Original Article

Colchicine Treatment in Children With Familial Mediterranean Fever: Is it a Risk Factor for Neuromyopathy?

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ABSTRACT

BACKGROUND: We cared for a 17-year-old adolescent with familial Mediterranean fever under colchicine treatment. Because of the increased creatinine kinase level (3937 U/L) observed in this individual, we planned to assess all pediatric patients with familial Mediterranean fever under colchicine treatment to detect any resultant neuromyopathy. **METHODS:** The study included 88 children with familial Mediterranean fever who were receiving colchicine. The patient with myopathy was not included in the study. Serum creatinine kinase levels were measured and nerve conduction studies were carried out in all patients. **RESULTS:** The study included 88 patients (47 female, 53.4%) with an average age of 10.1 ± 3.35 years. The average period of colchicine use was 28.25 ± 17.66 months. Side effects of colchicine were detected in 10 patients (11%)—as diarrhea in eight patients, leukopenia in one patient, and hair loss in one patient. Nerve conduction studies determined incidental carpal tunnel syndrome in only one patient. **CONCLUSIONS:** Our study did not suggest an elevated risk of neuromyopathy associated with the use of colchicine for familial Mediterranean fever.

Keywords: colchicine, familial Mediterranean fever, neuropathy, myopathy, children

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Introduction

Colchicine is usually prescribed for familial Mediterranean fever. The most frequent side effects of colchicine are nausea, abdominal pain, and diarrhea.[1] Colchicine can also cause a toxic neuromyopathy, which usually develops after chronic administration. Colchicine is known to bind tubulin and prevent its polymerization into microtubules, which are present in ciliary cells and leukocytes and are responsible for intracellular transport and cell motility. Lysosome and autophagic vacuoles stored in cells cannot be removed; permeability is increased due to damage to the lysosomal membrane, leading to neuropathy and/or myopathy.[2,3] Although both skeletal muscles and peripheral nerves are affected, myopathy is most prominent and associated axonal neuropathy is mild. Proximal weakness is a common symptom of myopathy. Several risk factors promote neuromyopathy, such as chronic renal failure, hepatic failure, and drug interaction. Patients usually manifest with progressive proximal muscle weakness over several months. Although myopathy regresses from 3 to 4 weeks after cessation of the drug therapy, the neuropathy has a more persistent clinical course.[4-8]

The literature includes no data about the frequency of neuromyopathy associated with colchicine use in patients with familial Mediterranean fever. This study examined the frequency of neuropathy and myopathy associated with colchicine in pediatric patients receiving colchicine treatment for familial Mediterranean fever.

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Patients and Methods

The study was approved by the Ethics Committee of the University of Gaziantep, and written informed consent was obtained from the children's parents.

Selection of patients

The study included 88 individuals who used colchicine for familial Mediterranean fever and who were followed by the Pediatric Nephrology Outpatient Clinic in the Department of Pediatrics, Faculty of Medicine, Gaziantep University, between 2010 and 2012.

Preparation of patients

Patients' medical histories were reviewed before nerve conduction studies (NCS). All patients were examined for neuropathy and myopathy findings. Neurologic examinations were conducted in the Child Neurology Polyclinics, and electrophysiologic evaluations were conducted in the Electrophysiology Laboratory of the Neurology Department. Serum creatinine kinase (CK) levels were measured in all patients.

Conducting the study

NCS of all patients were performed using a Medtronic Keypoint electroneuromyography (ENMG) device. Motor NCS, including *F* waves, were performed for the median, ulnar, peroneal, and tibial nerves; sensory NCS were performed for the median, ulnar, and sural nerves unilaterally. All studies were carried out using surface recording electrodes.

Statistical analysis

Descriptive demographical data of the patients were analyzed via the Statistical Package for the Social Sciences 15.0. Numerical values are shown as average ± standard deviation or the number of cases (%).

Results

The study included 88 pediatric patients with familial Mediterranean fever who were receiving colchicine treatment; 53.4% (n = 47) of the patients were female, and the average age of patients included in the study was 10.1 ± 3.35 years (2.4-18.9). The average age at the time of familial Mediterranean fever diagnosis was 7.74 ± 3.29 years (1.7-15). All patients started colchicine treatment after their diagnosis. Colchicine dosages were as follows: 72% used 0.01 mg/kg, 12.5% used 0.005 mg/kg, 12.5% used 0.015 mg/kg, and 3% used 0.03 mg/kg. The average duration of colchicine usage was 29.06 ± 19.58 months. Mean CK value among all patients was 97.57 ± 38.76 U/L (17-185).

None of the study patients had experienced complications such as amyloidosis, renal insufficiency, or familial Mediterranean fever seizure when included in the study, and none reported any other complaints. Colchicine side effects were determined in 10 (11%) patients—as diarrhea in eight patients, leukopenia in one patient, and hair loss in one patient. Decreased colchicine dosage subsequently resolved the complaint of diarrhea within approximately 1 week. Leukopenia was temporary, and the patient recovered spontaneously in 10 days.

One patient had been followed for myopathy even before the present study. This patient was a 17-year-old male. He was diagnosed as familial Mediterranean fever at the age of 61 months and received colchicine treatment (0.016 mg/kg). High asymptomatic CK level (3937 U/L) was determined during routine observations in the second year of colchicine treatment. Neurological and other systemic examinations during this period were normal, as were NCS. However, needle ENMG could not be conducted because the patient withheld consent. Nonspecific myopathic changes were determined in the muscle biopsy pathology. A limited decrease in CK values was observed when colchicine treatment was ceased for 5 months (2341 U/L in the first month, 2542 U/L in the second, 1556 U/L in the third, and 1926 U/L in the fifth); however, colchicine treatment (0.016 mg/kg) was restarted when familial Mediterranean fever attacks became frequent. CK levels rose to their previous levels with the colchicine treatment (3938 U/L).

NCS were within normal limits in all patients examined, except for one patient with mild incidental carpal tunnel syndrome (CTS). This was a 17-year-old male. He was diagnosed as familial Mediterranean fever and started colchicine treatment (0.016 mg/kg) because of frequent abdominal pain and febrile attacks for 5-6 months when age 11 years. NCS of the patient during the third year of familial Mediterranean fever diagnosis found low sensorial nerve conduction rates in the palm/wrist segment of the median nerve in both hands; however, it was higher in the right hand (33 m/second on the right, 39 m/second on the left). In addition, sensorial nerve amplitude was low in the right hand (3.1 μV) and normal in the left hand (7.3 μV). Other nerve conduction tests (motor and sensorial) were normal. The patients' NCS results are shown in Tables 1 and 2.

Discussion

Colchicine has the potential for serious side effects, including neuromyopathy. There are also concerns about a potential association between colchicine and neuromyopathy, but studies in the literature are lacking.[1] Asymptomatic elevated CK was determined in the index case upon which the present study is based. Myopathy could not be definitively linked with colchicine in this case. However, in symptomatic patients who develop myopathy as a result of colchicine use, serum CK levels could increase 50 times, whereas in asymptomatic patients, this increase

TABLE 1.
Motor nerve conduction studies of patients

Nerve	Distal Latency	Amplitude	Conduction Velocity	*F* Wave
Median	3.4 (2.8-4.1)	8.2 (6.1-11.3)	54.2 (50.2-63.2)	27.5 (24.6-31.6)
Ulnar	2.7 (2-3.5)	9.6 (7.3-13.1)	55.0 (51-59.6)	28.0 (25.1-31.7)
Tibial	5.3 (3.2-5.9)	10.8 (6.2-19.7)	45.1 (40.7-54.2)	49.2 (46.1-54)
Peroneal	4.4 (3.1-5.8)	5.5 (2.6-11.5)	46.2 (41.1-54.4)	48.4 (42.3-54.5)

Values are expressed as mean (range). Distal latency and *F* wave are expressed in ms. Amplitude is expressed in mV. Conduction velocity is expressed in m/second.

TABLE 2.
Sensory nerve conduction studies of patients

Nerve	Amplitude	Conduction Velocity
Median	36.5 (15.8-118)	54.0 (44.2-62)
Ulnar	38.2 (13.2-103.4)	55.1 (50-61.1)
Sural	13.1 (6.2-24)	47.3 (40.2-59.3)

Values are expressed as mean (range). Amplitude is expressed in mV. Conduction velocity is expressed in m/second.

may be much smaller. The findings in patients developing myopathy return to normal levels 4-6 weeks after ceasing colchicine.[5-9]

In the present study, NCS identified asymptomatic CTS in only one patient. As in this patient, previous studies have reported that only sensorial conduction abnormality is observed.[10] In addition, CTS is known to possibly develop secondarily to systemic amyloidosis.[11,12] Amyloidosis is clinically observed with proteinuria,[13] which was not determined during the follow-up of the patient. Therefore, amyloidosis-related CTS was not considered in this patient. We were unable to determine a relationship between the CTS development and colchicine use and familial Mediterranean fever, or any etiological cause of the CTS, in this patient.

Our results indicate that colchicine-dependent neuromyopathy is not a commonly observed complication in children. In addition, it should be considered that patients using statins or drugs with myopathic side effects such as chronic kidney failure may develop colchicine-dependent neuromyopathy.[14,15] In the present study, neuromyopathy could not be determined in 10 patients developing colchicine-related side effects. Patients with complaints such as muscular pain, loss of strength, and numbness in the extremities may develop colchicine-dependent neuromyopathy. Routine ENMG follow-up is not rational for asymptomatic patients using colchicine who do not have any risk for colchicine toxicity. Clinical and infrequent CK follow-up would be reasonable in such patients.

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