Colchicine Therapy and the Cognitive Status of Elderly Patients with Familial Mediterranean Fever

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Abstract

Backgound: Colchicine is widely used for treating gout and familial Mediterranean fever. However, studies in animal models have reported ill effects of colchicine on the central nervous system, including cognitive function.

Objectives: To evaluate the cognitive status of elderly FMF patients on long-term colchicine treatment.

Methods: The study group consisted of 55 FMF patients aged 74 ± 5, attending an FMF outpatient clinic and receiving colchicine treatment for 25.1 ± 8.9 years. The Mini-Mental State Examination was used for cognitive evaluation. Patients' scores were compared with accepted age- and education-adjusted cutoff scores, population-based norms, and scores of a matched control group of 56 subjects.

Results: Individually, all colchicine-treated FMF patients scored well above the age- and education-corrected cutoff scores. Overall, there was a large difference, 5.0 ± 1.6, from the expected cutoff points, in favor of the study group scores ($P < 0.001$). The individual scores of the control group were also above the cutoff points, however with a lower but still statistically significant difference (3.71 ± 1.15 points, $P < 0.001$). Compared to population-based norms adjusted by age and education, the study group had significantly higher mean MMSE scores (27.2 ± 2.2 vs. 25.5 ± 2.4, $P < 0.001$). The control group's scores were also somewhat higher than expected, but not significantly so.

Conclusions: Our results do not support the view that prolonged colchicine treatment may be associated with cognitive impairment. On the contrary, it is possible that long-term colchicine treatment may even confer protection against cognitive decline in patients with FMF.

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Colchicine, an alkaloid extracted from some plants of the lily family, has been used for centuries to treat acute gouty arthritis. Since 1973, it has been recognized as an effective remedy for prophylaxis of attacks of familial Mediterranean fever, and a decade later it came into use for the prevention of amyloidosis, a lethal complication of FMF [1,2]. FMF is an inherited disorder that occurs predominantly in patients of Arab, Armenian, and Sephardic Jewish ancestry. It is characterized by recurrent episodes of fever, arthritis, peritonitis and/or pleuritis, leading in some cases to amyloidosis and renal failure. In the majority, the symptoms begin between the ages of 5 and 15 [3]. Often, colchicine is used prophylactically for decades in these patients [1].

FMF = familial Mediterranean fever
MMSE = Mini-Mental State Examination

In animal models of central nervous system damage, colchicine, a microtubule-disrupting agent, is used as a neurotoxin. Following its introduction into the brain, colchicine binds to tubulin, the principal structural protein of the microtubule, and induces microtubular depolymerization and destabilization, with subsequent block of axonal transport and mitosis, resulting in neuronal cell death [4-7]. The neurotoxicity is mediated through free radical production and the resultant oxidative stress [6]. In addition, colchicine causes loss of cholinergic neurons, destruction of cholinergic pathways, and decrease in cholinergic turnover [4,8]. The distribution of colchicine in the brain is unequal; its concentration in the hippocampus, the area most affected in Alzheimer's disease, is almost three times higher than in other brain regions [9]. The drug selectively blocks acetylcholine transferase in the hippocampus and basal forebrain, the brain areas responsible for memory consolidation [8].

Clinically, the result of central colchicine administration is progressive deterioration of learning and memory, i.e., cognitive impairment [8-11]. The central manifestations of colchicine neurotoxicity in the animal model closely simulate Alzheimer's disease in humans [6,7,11]. Both are characterized by oxidative stress, microtubule disruption, decrease in cholinergic activity, and progressive deterioration of cognitive functions [5,10,11]. Systemic administration of colchicine in rats also induced cognitive defects similar to those of Alzheimer's and characterized by amnesia of recent learning and loss of formerly established memories [7].

To date, there are no published studies on the central nervous system effects of colchicine in humans, either with short-term oral use, e.g., for gout, or with long-term use, e.g., for FMF. The present study was designed to investigate the mental status of elderly FMF patients on long-term colchicine treatment.

Patients and Methods

The study group comprised the 55 FMF patients, aged 65 years or more, attending the FMF outpatient clinic at the Sheba Medical Center, Israel. They were all examined by physicians working in the FMF clinic (A.L., M.L.), and their compliance with the diagnostic criteria of FMF [12] and colchicine treatment was confirmed. Subsequently, they were interviewed by specialists in geriatric medicine (A.L., R.S.,Y.B.). This age group was chosen because of their vulnerability to cognitive deterioration [13], as well

as for the longer duration of colchicine treatment. The control group consisted of 56 subjects, aged 65 years or more, recruited randomly from among the 180 pensioners at our hospital, and matched by education, gender and ethnic origin. The controls were interviewed, by the specialists in geriatric medicine, during one of the bi-annual social gatherings organized for the pensioners by the hospital. None was on colchicine treatment.

Demographic data and a medical history, including drug treatment, were collected and a cognitive assessment test, the Mini-Mental State Examination, was administered. This is the most widely used screening test to detect cognitive impairment, with a relatively high sensitivity (80–85%) [14]. The study was approved by our ethics review committee and informed consent was obtained from each subject participating in the study.

Statistical analysis

SPSS software was used for statistical processing. Student's *t*-test and one-way ANOVA were used for comparison of averages. Pearson product-moment correlations were performed to evaluate confounding factors for MMSE scores, such as associated diseases, colchicine therapy, and use of aspirin and non-steroidal anti-inflammatory drugs.

The scores obtained by the participants of the study and the control group were compared, individually for each patient, to the available age- and education-adapted normal cutoff scores and to age- and education-corrected normal population mean scores [15,16]. Comparisons with the general population were also performed for the study and control groups as a whole, as well as for three age subgroups: 65–69, 70–74 and 75–79 years. Finally, the scores of the FMF patients were compared with those of the controls.

Results

The bulk of relevant clinical and demographic data are presented in Table 1. Among the study group patients, 95% had been taking colchicine for more than 10 years, 75% for more than 20 years and 36% for 30 or more years. Forty-six percent took 1 mg colchicine daily, 24% took 1.5 mg and 27% took ≥ 2 mg (maximum daily dose being 2.5 mg). With regard to associated diseases and aspirin use, the control group did not differ significantly from the FMF patients. None of the patients or controls habitually used NSAIDs.

Individually, none of the patients failed the MMSE: all were well above the cutoff points of the age- and education-corrected scores [Table 2]. Seen as a whole, there was a wide and positive gap, 5.0 ± 1.6 points ($P < 0.001$), between the study group's mean MMSE score and the mean cutoff score expected for an adjusted population. The scores of all subjects in the control group were also above the adjusted general population cutoff points, however with a somewhat smaller difference, 3.71 ± 1.15 ($P < 0.001$). The mean MMSE scores of the control group as a whole, as well as those of its age subgroups, were lower than those of the colchicine-treated FMF patients, reaching significance only in the 70–74 year old age subgroup [Table 2].

Compared to population-based norms by age and education, the study group as a whole, as well as the various age-derived subgroups, had significantly higher mean MMSE scores [Table 2]. Individually, only two patients had somewhat lower scores. The control group's scores were also above the norms, but not significantly so. Individually, the scores of five control subjects were below the norms. No correlation was detected between length of colchicine use or dosage, and MMSE scores. No confounding factors, such as associated diseases and aspirin use, were found to affect the MMSE scores.

Table 1. Demographic data of participants*

	Patients (n=55)	Controls (n=56)
Males	22	20
Mean age (yrs)	71.3 ± 4.86	71.7 ± 4.5
Education (yrs)	8.5 ± 1.9	9.3 ± 2.5
Origin (%)		
Middle East	86	80
Europe	14	20
Years of colchicine use	25.1 ± 8.9	
Mean daily colchicine dosage (mg)	1.4 ± 1.2	
Mini-aspirin therapy (%)	24	20
Hypertension (%)	34	30
Ischemic heart disease (%)	27	25
Diabetes mellitus (%)	9	12
Hyperlipidemia (%)	7	11
Cerebrovascular accident (%)	4	2

* The differences between patients and controls were not statistically significant

Table 2. Mini-Mental State Examination in colchicine-treated elderly FMF patients

Age group (yrs)		No. of participants	Mean MMSE score of participants	Mean population-based MMSE* norms	P
65–69	FMF	23	27.2 ± 2.6	25.5 ± 2.8	0.000
	Controls	24	26.7 ± 2.4	26.7 ± 2.3	NS
70–74	FMF	19	28.0 ± 1.2**	26.1 ± 1.6	0.000
	Controls	18	27.1 ± 1.2	26.8 ± 0.4	NS
75–79	FMF	13	26.1 ± 2.2	24.6 ± 2.4	0.011
	Controls	14	26.1 ± 1.8	26.0 ± 1.2	NS
Total	FMF	55	27.2 ± 2.2	25.5 ± 2.4	0.000
	Controls	56	26.7 ± 2.0	26.5 ± 1.7	NS

* Age and education adjusted.

** $P < 0.05$, mean MMSE score of FMF patients vs. controls.

P = mean MMSE scores of participants vs. mean population-based MMSE norms by age and educational levels

Discussion

The results of this study show that prolonged treatment with colchicine did not interfere with the cognitive function of elderly FMF patients. On the contrary, their scores were significantly higher than the mean population-based MMSE norms adjusted

NSAIDs = non-steroidal anti-inflammatory drugs

for age and education. Their scores were also higher than those of the controls, though not significantly so (except in one of the age subgroups).

Despite the concerns arising from animal models regarding colchicine neurotoxicity, our results suggest that no deleterious cognitive effects are associated with prolonged use of this drug. A possible explanation may be the fact that colchicine, although highly lipophilic, has poor penetration through the blood-brain barrier. P-glycoprotein, an ATPase-dependent efflux pump of the capillary endothelial cells at the brain surface, may be responsible for this poor access [17,18]. This raises doubts regarding the use of colchicine concomitantly with drugs such as calcium channel blockers, phenothiazines, quinolones, cefoperazon, rifampin, corticosteroid and the new antidepressants (sertraline, desmethylsertraline, paroxetine). These drugs are known as "reversal agents" because of their ability to inhibit P-glycoprotein activity [19,20]. Further studies regarding possible drug-drug interaction within this context are warranted.

Within the limitations of this study – namely, a relatively small sample size and the use of a screening procedure rather than a definitive test for detection of cognitive impairment – we may conclude that even with very long-term use (decades), no discernible deleterious central nervous system effects of colchicine have been detected.

At this point we should relate to some disparities between the studies mentioned and the human subjects in the study. The majority of the animal studies were performed on rats and the authors did not report their age. However, old-aged animals are not routinely used for research without specification. As for site and dose of administration, in most studies [6,7,10,11] colchicine was administered locally (intracerebrally, intraventricularly, intraperitoneally). The only study in which the drug was injected intravenously used very high doses [9]. Indeed, the human subjects in our study ingested relatively small doses of the drug but they did it for a very long period (on average 25 years).

The prospect of a protective effect of colchicine against cognitive deterioration is tempting. In this context it is notable that colchicine was proposed and tested in a pilot tolerability study as a possible prophylactic treatment of Alzheimer's disease [21]. This approach was based on the anti-inflammatory effect of colchicine on the one hand, and the extensive experimental evidence of inflammatory mechanisms that contribute to neuronal cell loss in Alzheimer's, on the other [22]. Moreover, one study reports that the beta-amyloid neurotoxicity, which is considered a basic pathogenic process in Alzheimer's disease, can be inhibited by colchicines [23]. Other anti-inflammatory drugs, such as NSAIDs, were also found to be of potential value for the prevention of Alzheimer's disease [24].

In conclusion, this study does not support the view that cognitive impairment may be associated with prolonged colchicine treatment. In fact, the reverse was true: our FMF patients on long-term colchicine therapy had better than expected cognitive performance. Future studies, on larger cohorts and using definitive diagnostics rather than screenings for detection of dementia, are needed to consolidate our results.

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