Colchicine in stroke prevention. Is it time to change our clinical practice?

Colchicina en prevención del ictus. ¿Es hora de cambiar nuestra práctica clínica?

Dear Editor:

Colchicine is an old drug with several anti-inflammatory properties that has traditionally been used to treat various rheumatic disorders (for example, gout and Behçet disease, among others).[1] Specifically, it prevents the development of microtubules by inhibiting leukocyte function, and blocks the assembly of the NOD-like receptor P3 (NLRP3) inflammasome, preventing the release of IL-1β and the expression of other proinflammatory cytokines, some of which are known to play a role in cerebrovascular disease, such as MMP-9.[2,3]

Colchicine is used similarly to statins in the prevention of ischaemic stroke. Thus, in the Scandinavian Simvastatin Survival Study (4S), the first randomised prospective trial of a statin, simvastatin not only decreased overall mortality (30%) and the frequency of coronary events (34%), but also the frequency of stroke (30%).[4]

It should be noted that all patients in the 4S trial presented coronary artery disease (CAD). Furthermore, the majority of trials addressing the secondary prevention of CAD (4S, CARE, LIPID, GREACE, and TNT) found statins to be beneficial in stroke prevention. Finally, in the SPARCL trial, the first trial of secondary stroke prevention in patients without CAD, atorvastatin significantly reduced stroke.[5]

In this regard, colchicine has emerged as a therapeutic option for the secondary prevention of cardiovascular disease in patients with CAD.

Over the past 3 decades, several observational and randomised studies have assessed the impact of colchicine in patients with CAD and shown a reduction in the frequency of ischaemic events, including revascularisation, myocardial infarction, and also stroke or transient ischaemic attack (TIA).[2,3]

Similarly, patients surviving ischaemic stroke present greater risk of new events, approximately 30% at 5 years, partly due to arterial inflammation,[6] also known as residual inflammatory risk.[7]

Thus, therapies specifically aiming to treat the inflammatory risk may decrease the rate of recurrent events. In the paradigmatic CANTOS trial, inhibition of the NOD-like receptor protein 3 inflammasome using the anti—IL-1β monoclonal antibody canakinumab decreased the rate of cardiovascular events in patients with elevated high-sensitivity C-reactive protein test results, also showing a possible 30% reduction in the risk of stroke.[7]

In fact, in a recent prospective multicentre cohort study of 10 499 patients with ischaemic stroke or TIA, residual inflammatory risk (defined as presenting an LDL cholesterol level < 100 mg/dL and high-sensitivity C-reactive protein level ≥ 3 mg/L) was associated with recurrent stroke (hazard ratio, 1.18; 95% CI, 1.00-1.40).[8]

A systematic review and meta-analysis of randomised controlled trials showed that the decrease in severe cardiovascular events with colchicine was greatest for stroke, with reductions in risk of 62%, 44%, and 38% for ischaemic stroke, emergency coronary revascularisation, and myocardial infarction, respectively.[2]

Another recent meta-analysis of randomised controlled clinical trials including 6630 patients at high cardiovascular risk specifically analysed the role of colchicine in stroke prevention. The use of colchicine led to a significant reduction in the risk of stroke (odds ratio, 0.33; 95% CI, 0.15-0.70).[9]

Colchicine would reduce not only the growth of the plaque,[2,3] but also the risk of atrial fibrillation,[10] and even prevent both the progression of the peripheral vascular disease at the carotid level[11] and the progression of aortic aneurysms, by inhibiting the degradation of the extracellular matrix.[12]

Several clinical trials are currently assessing the usefulness of colchicine in the prevention of vascular events after a stroke or TIA. Thus, the CONVINCE trial, which includes 3154 patients with non-cardioembolic stroke or high-risk TIA, aims to determine whether adding colchicine to the standard treatment leads to a reduction in the recurrence of stroke and vascular events.[13]

In the meantime, the 2021 guidelines of the European Society of Cardiology recommend for the first time the use of anti-inflammatory treatment for the secondary prevention of atherosclerosis. They recommend considering low-dosed colchicine (0.5 mg once daily) for the secondary prevention of cardiovascular disease when other risk factors are not sufficiently controlled, or if recurrent events occur despite optimal treatment (grade of recommendation IIb, level of evidence I).[14]

Therefore, colchicine, a safe and frequently used anti-inflammatory drug that inhibits the inflammation associated with vascular disease, creates a new paradigm in the prevention of atherosclerotic ischaemic stroke. We may soon see a new change in our clinical practice.

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DOI of original article: https://doi.org/10.1016/j.nrl.2022.03.001.

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10 December 2021

Impact of age and education on performance in the Spanish-language version of the Edinburgh Cognitive and Behavioural ALS Screen in a cohort of patients with amyotrophic lateral sclerosis

Influencia de la edad y la escolaridad sobre el rendimiento de la versión española del *Edinburgh Cognitive and Behavioural ALS Screen* en una cohorte de pacientes con esclerosis lateral amiotrófica

Introduction

In recent years, growing evidence has been reported on the presence of non-motor symptoms in amyotrophic lateral sclerosis (ALS), such as those affecting cognition. Between 30% and 50% of patients with ALS may present cognitive disorders[1,2], and approximately 15% meet diagnostic criteria for frontotemporal dementia[3]. These patients' cognitive profile is characterised by deficits in executive function (especially in fluency), language, social cognition, and verbal memory[1]. The Edinburgh Cognitive and Behavioural ALS Screen (ECAS)[4] is a screening tool designed to asses behavioural alterations and cognitive performance in multiple domains in patients with ALS. The ECAS has been validated in a Spanish population and cut-off scores have been established[5]; however, age- and education-adjusted cut-off scores are yet to be published. Sociodemographic variables should be considered due to their impact on ECAS scores.

DOI of original article: https://doi.org/10.1016/j.nrl.2022.02.003.

This study aims to analyse the association between these sociodemographic factors and ECAS scores in a cohort of patients with ALS.

Methods

We collected clinical and sociodemographic data and ECAS scores from a cohort of patients with ALS (probable/definite ALS according to the El Escorial criteria) from our centre. We gathered total ECAS scores, ALS-specific ECAS scores (including the cognitive domains of language, fluency, and executive functions), ALS-nonspecific ECAS scores (including memory and visuospatial functions), and individual ECAS domain scores. We calculated the Spearman correlation coefficient to analyse the association between education level and ECAS scores, and the Mann-Whitney U test and effect sizes (Hedges' g) were used to compare groups in terms of age (< 65 vs $\geq$ 65 years, based on the established age limit of onset of neurodegenerative diseases) and education (< 10 vs $\geq$ 10 years of schooling).

Results

Our sample included 23 patients (60.9% men; mean age, 63.9 $\pm$ 11.46 years; mean years of schooling, 10.2 $\pm$ 4.48); 20 (86.96%) had spinal-onset ALS and 3 (13.04%) had bulbar-onset ALS. Age and education level were significantly correlated with total ECAS score (Spearman rho = —0.593; P = .003 and rho = 0.691; P < .001, respectively) (Fig. 1), ALS-specific ECAS score (rho = —0.610; P = .002 and rho = 0.681; P < .001, respectively), and ALS-nonspecific ECAS score (rho = —0.436; P = .037 and rho = 0.519; P = .011, respectively), as well as with individual ECAS domain scores (age: rho = —0.521 to —0.608; $P \leq .05$; education level: rho = 0.428 to 0.674; $P \leq .05$). Table 1 compares ECAS scores between age and education groups, providing effect sizes. We found significant differences ($P \leq .05$) in ECAS scores between patients younger than and older than 65 years (except for ALS-nonspecific ECAS scores: P = .201) and between patients with less than or more than 10 years of schooling (except for ECAS fluency score: P = .092). The effect size was moderate for differences between age groups in ALS-nonspecific ECAS score and ECAS visuospatial score (g = 0.61 and g = 0.56, respectively) and for differences between education groups for ALS-