Case report

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Off-label use of eculizumab for neurological symptoms and progressive vision loss

Alicja Kuźniewska[1*], Marta Jaskólska[2*], Mariusz Kwarciany[3], Aleksandra Ciarka[4], Rafał Pęksa[4], Zbigniew Zdrojewski[2], Marcin Okrój[1]

[1]Department of Cell Biology and Immunology, Intercollegiate Faculty of Biotechnology, University of Gdańsk and Medical University of Gdańsk, Poland, [2]Department of Rheumatology, Clinical Immunology, Geriatrics and Internal Medicine, Medical University of Gdańsk, Poland, [3]Department of Neurology, Division of Adult Neurology, Medical University of Gdańsk, Poland, [4]Department of Pathomorphology, Medical University of Gdańsk, Poland

[*]AK and MJ equally contributed as the first authors.

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Abstract

We describe the results of eculizumab treatment of a patient with pachymeningitis, inflammatory infiltration of the left frontal lobe, and cerebral hematoma, who presented with progressive vision loss, epileptic seizures, and abnormal pattern of the complement system parameters. A 30-year-old female patient, initially diagnosed with hypereosinophilia and a tumour of the left orbit, developed a significant visual impairment in the left eye, progressive vision loss in the right eye, and neurological symptoms in the form of epileptic seizures and behavioural changes. Magnetic resonance imaging (MRI) revealed thickening of the dura mater in the left frontal area, slight oedema of the cortex, and subcortical white matter. Orbit biopsy showed non-specific inflammatory infiltrates. Despite the initial good response, symptoms progressed during treatment with glucocorticoids and immunosuppressants. Increased activity of the alternative complement pathway accompanied by a low level of its main inhibitor, factor H (FH), and the presence of anti-FH autoantibodies, was found. Genetic analysis revealed several missense variants of complement proteins, including two disease-linked mutations in FH (p.H402Y) and FI (T300A). An attempt to apply a complement C5 blocker, eculizumab, has been made. Neurological symptoms subsided, vision loss was inhibited, laboratory parameters improved, and discontinuation of steroid therapy was possible. The case underlines the role of complement system dysregulation in neurological distress.

Key words: *eculizumab, complement system, epilepsy, cerebral hematoma, vision loss.*

Introduction

Eculizumab is a monoclonal antibody that blocks the terminal pathway of the complement cascade at the level of C5. Its clinically approved indications include paroxysmal nocturnal haemoglobinuria, atypical haemolytic uremic syndrome, generalized myasthenia gravis, and neuromyelitis optica spectrum disorder [5]. Despite substantial costs for healthcare providers, numerous successful off-label applications of eculizumab were reported, as the complement system is involved in the pathogenesis of multiple disorders and fuels unwanted inflammation [1,10,11,13,16]. Herein, we present the case of a 30-year-old female patient with inflammatory orbital pseudotumor, who subsequently developed pachymeningitis. Her clinical picture was dominated by the involvement of the orbit and central nervous system leading to progressive vision loss and epilepsy. We describe the path that brought us to the off-label application of eculizumab, which pro-

Communicating author:
Marcin Okrój, Department of Cell Biology and Immunology, Intercollegiate Faculty of Biotechnology, University of Gdańsk and Medical University of Gdańsk, 1 Dębinki St., 80-211 Gdańsk, Poland, phone: +48 583491410, e-mail: marcin.okroj@gumed.edu.pl

vided a substantial improvement. The additional period of time allowed for the extension of diagnostics and finally immunoglobulin G4 (IgG4)-related disease was diagnosed.

Case description

In 2014, the patient was diagnosed with hypereosinophilia, manifested by localized tissue swelling, urticaria, and erythema multiforme. Chronic eosinophilic leukemia and other lymphoproliferative diseases were excluded. Remission was achieved on glucocorticoid (GCS) therapy and since then, due to the diagnosis of the hypereosinophilic syndrome, the patient has been periodically treated with GCS. Since 2014, the patient had recurrent scleritis and episcleritis which eventually led to a decrease in visual acuity in the left eye and then in the right eye. In 2015, she was diagnosed with a pseudotumor of the left orbit. The histopathological examination of the tissue revealed the presence of non-specific lymphocytic and plasmocytic infiltrates. In February 2019, the patient experienced the first focal to bilateral tonic-clonic seizures, later on treated symptomatically with antiepileptic drugs. In January 2021, neurological symptoms worsened. The patient complained about headaches, increased frequency of epileptic seizures, and behavioural changes. At that time, a slight increase in inflammatory parameters was observed, while eosinophilia was not present in the peripheral blood. Brain magnetic resonance imaging (MRI) showed a hyperintense area in the left frontal lobe causing a mass effect. The lesion decreased after treatment with dexamethasone, but the control MRI showed pathological thickening and post-contrast enhancement of the dura mater and leptomeninges limited to the left frontal area (Fig. 1A). At that time the patient did not consent to the biopsy.

The diagnostics for autoimmune/rheumatic diseases showed negative results for anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA) and anti-phospholipid antibodies (APLA). Serum IgG4, and C3 and C4 complement components were normal, and tryptase was repeatedly negative. Parasitic infections were excluded. Additional tests of the complement system in serum were performed and revealed elevated activity of the alternative pathway (AP50 score 175%, normal range 50-113%), and decreased concentration of the main inhibitor of the alternative pathway, factor H (FH; 50.5 µg/ml, normal range 108-510 µg/ml). Additionally, we detected the presence of IgG antibodies against FH (15.0 U/ml, normal range < 10 U/ml) (Fig. 2). The markers of the complement activation: Bb (8.4 µg/ml) and sTCC (1300 ng/ml), were also above the normal range (< 6.26 µg/ml and < 525 ng/ml, respectively),

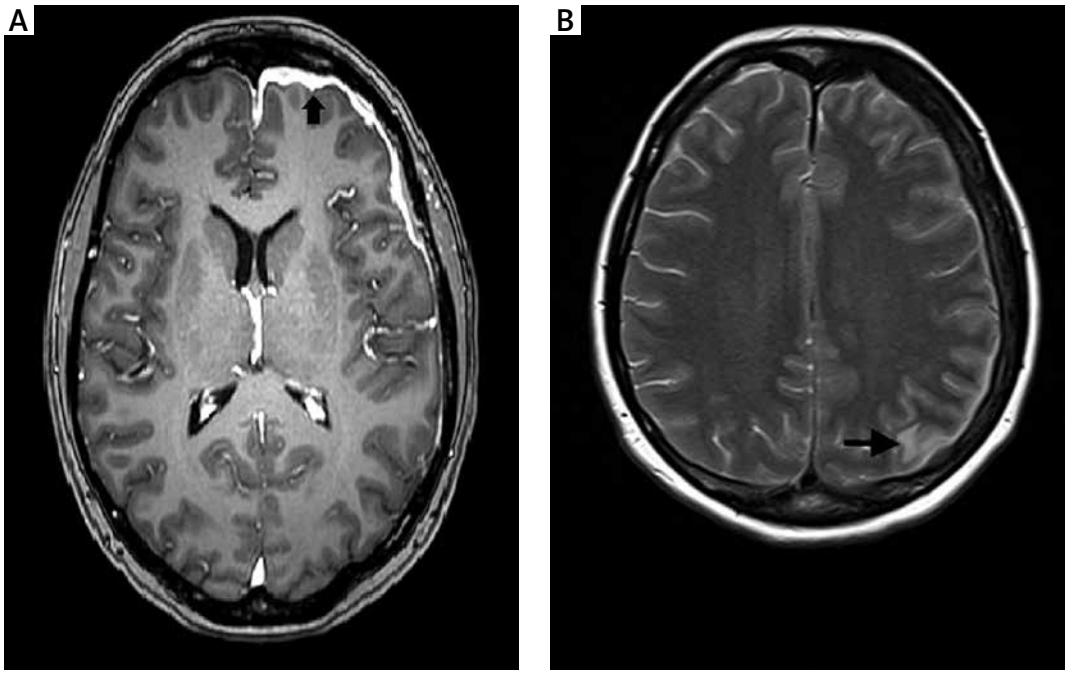

Fig. 1. Magnetic resonance imaging of the patient's brain. **A**) At the level of the frontal lobe of the left hemisphere of the brain, thickening and pathological signal of the meninges are visible. **B**) A small area of malacia in the left parietal lobe, probably after an ischemic episode.

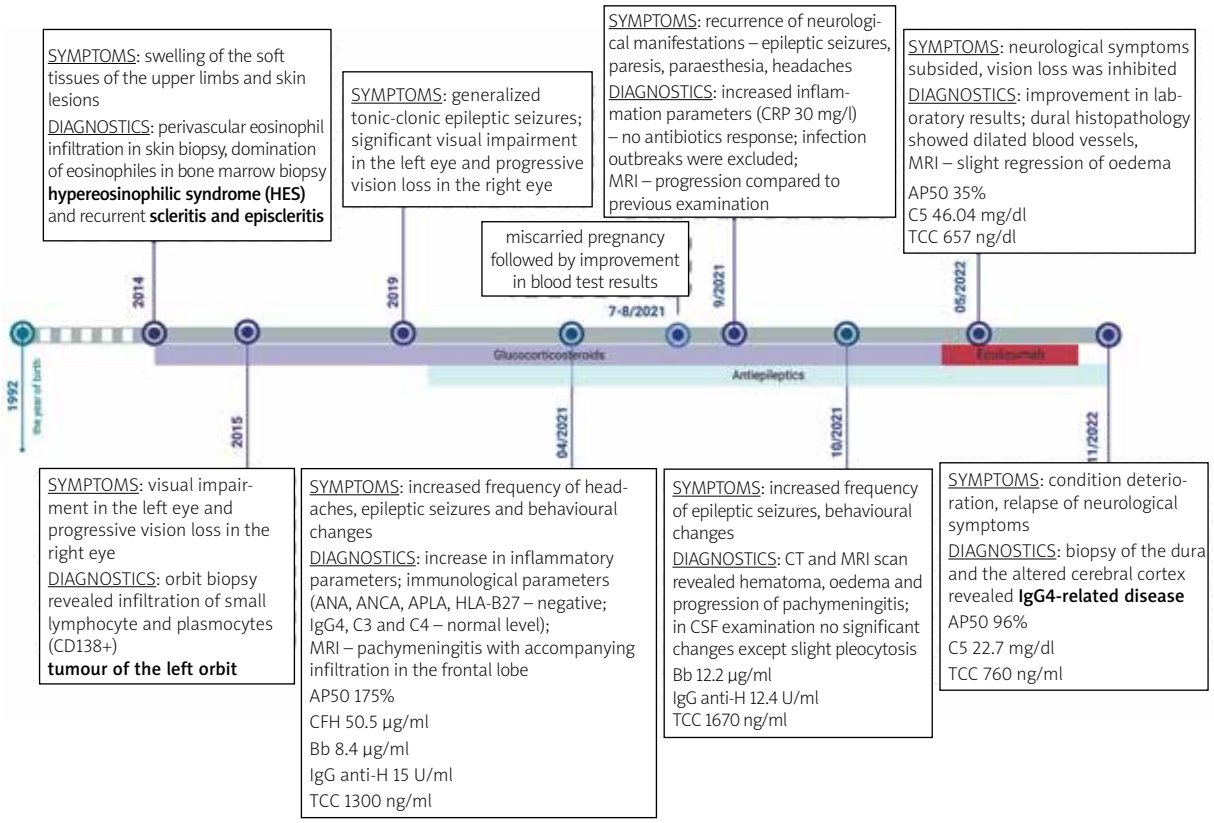

Fig. 2. Timetable of the patient's symptoms, diagnosis, eculizumab treatment, and related laboratory parameters of the complement system. Only the complement system parameters that exceeded reference values are presented. Acronyms: AP50 – activity of the alternative complement pathway (ref. 50-113%), CFH – complement factor H (ref. 108-510 mg/ml), Bb – fragment b of the complement factor (activation marker, ref. 0.8-6.2 mg/ml), TCC – terminal complement component (activation marker, ref. 127-528 ng/ml), IgG anti-FH – IgG antibodies against complement factor H (ref. < 10 U/ml), C5 – complement component 5 (ref. 9.8-19.3 mg/dl).

however, the credibility of these two latter measurements in serum is debatable, and no EDTA-plasma samples were available at this time point (Fig. 2).

So far, the differential diagnosis has included eosinophilic granulomatosis with polyangiitis (EGPA). However, the clinical course was atypical (no asthma, peripheral neuropathy, previous biopsy results inconclusive), and IgG4-related disease (IgG4 in the serum within the normal range). In order to complete the diagnosis, a re-evaluation of the histopathological samples (orbital pseudotumor biopsy) was performed – IgG4 expression was absent in the inflammatory infiltrates. Despite the use of the GCS therapy, which initially brought a positive effect, a gradual progression of the disease was observed. Involvement of the immune mechanism was suspected due to the constantly abnormal parameters of the complement system. Follow-up brain MRI revealed progression of the pathological thickening and post-contrast enhancement of the dura mater and leptomeninges in the left frontal lobe, accompanied by slight oedema of the cortex and subcortical white matter. A dural biopsy was scheduled, but the procedure was abandoned due to a confirmed pregnancy. Due to the pregnancy, lack of final diagnosis, suspected immunological mechanism of the observed symptoms, it was decided to start a small dose of prednisone and additionally low molecular weight heparin in a prophylactic dose due to its additional complement inhibition mechanism within the placenta. There was a spontaneous miscarriage prior to the initiation of the above treatment.

In September 2021, in the period without immunosuppressive treatment, there was a recurrence of neurological symptoms – paresis of the right upper limb, paraesthesia in the left lower limb, headaches, epileptic seizures. Symptoms were preceded by an increase in C-reactive protein (CRP) to about 30 mg/l (no decrease after empiric antibiotic therapy). Dexamethasone was

Table I. Mutations in complement genes revealed in whole exome sequencing of the patient's DNA

Chromosome position	Gene symbol	Transcript	cDNA substitution	Amino acid substitution	Minor allele frequency	Zygosity
1:56956811	C8B	ENST00000371237	G416A	G117R	0.014	Homozygous
1:196690107	CFH	ENST00000367429	C1279T	H402Y	0.266	Heterozygous
1:196905226	CFHR4	ENST00000608469	G474T	E125D	0.006	Homozygous
1:207609571	CR1	ENST00000367049	A6289T	S2060T	0.005	Homozygous
1:207480050	CR2	ENST00000367057	C2376A	A1062E	0.057	Heterozygous
4:109757769	CFI	ENST00000645635	A926G	T300A	0.03	Homozygous
9:134909468	FCN1	ENST00000616356	T791C	L262S	Unknown	Homozygous
9:136946091	C8G	ENST00000371634	A431G	D118G	0.033	Homozygous

added in a dose of 4 mg twice a day, which resulted in clinical improvement. Brain MRI showed progression compared to previous examinations.

Suspecting the immune mechanism of the observed clinical symptoms, it was decided to intensify the immunosuppressive treatment – cyclophosphamide was added to the GCS, but due to poor tolerance of the drug, it was switched to azathioprine. Despite the treatment, the neurological symptoms progressed (increased frequency of epileptic seizures, behavioural changes) and at the end of October 2021, the patient was admitted to the hospital. Brain MRI revealed features of pachymeningitis with progression in comparison to previous studies, a small subdural hematoma at the level of the left frontal and parietal lobe, oedema of the left frontal lobe, and a small (10 × 14 mm) area in the left parietal lobe corresponding to an ischemic lesion (Fig. 1B). Due to the features of increased intracranial pressure, the lumbar puncture was performed by a neurosurgeon. The results of the CSF examination included: pleocytosis 11 cells/ul, mainly lymphocytes in the smear, negative infectious neuropanel, negative culture, and few small lymphocytes in the cytology of the sludge. Additionally, antibodies against AQP4 and MOG were negative. During hospitalization, dexamethasone and diazepam were used, and the dosage of levetiracetam was increased. Laboratory parameters still showed dysregulation of the complement system that could fuel inflammation (Fig. 2). Additionally, whole exome sequencing revealed eight missense variants in complement genes including six variants of unknown significance (VUS) and two disease-linked polymorphisms: 1) FH p.H402Y that results in impaired binding of this main soluble inhibitor of the alternative complement pathway, to heparan sulfate [4,8], and 2) complement factor I (CFI) p.T300A that results in the lower rate of C3b to iC3b processing [9] (Table I). Therefore, an attempt has been made to treat the patient with eculizumab, an inhibitor of the complement system. A six-month supply of the drug was granted in the framework of the Emergency Access to Drug Technology program (Polish acronym – RDTL). During the treatment, neurological symptoms subsided, vision loss was inhibited and laboratory improvement was achieved. It was possible to discontinue the steroid therapy, which was already starting to show side effects. Due to the features of slight progression of dural thickening in the control brain MRI, a decision was made to perform a biopsy. The histopathological examination revealed numerous dilated blood vessels but no specific infiltrates (Fig. 3A). During six months of treatment with eculizumab, the patient did not experience a relapse of neurological symptoms, however, her status markedly worsened after eculizumab discontinuation.

The treatment break was used to repeat the biopsy of the dura and the altered cerebral cortex. The final diagnosis based on the histopathological examination was IgG4-related disease (Fig. 3B-D). Previous biopsies were non-diagnostic most likely because they were performed during treatment.

Discussion and conclusions

The atypical clinical picture of our patient was dominated by neurological symptoms, behavioural changes, loss of vision, and dural thickening eventually connected to plasma cell infiltration and IgG4 deposits. In our opinion, complement overactivation was not the primary causative factor for most of the observed changes but rather a secondary event or an important comorbidity condition, inhibition of which eased the symptoms in this patient with such a complex disease. It is unlikely that IgG4 systematically activated the classical complement pathway (CP). First, they were not elevated in serum but only found locally at the examination of the dura biopsy. Then, we performed laboratory assays comparing the CP activation marker C4d [3] as well as a functional assay for the CP convertase activity [2] and did not find any significant difference between our patients and healthy donors. After all, human IgG4 antibodies have a very low potential of complement activation, compared to IgG1 or IgG3. There are reports

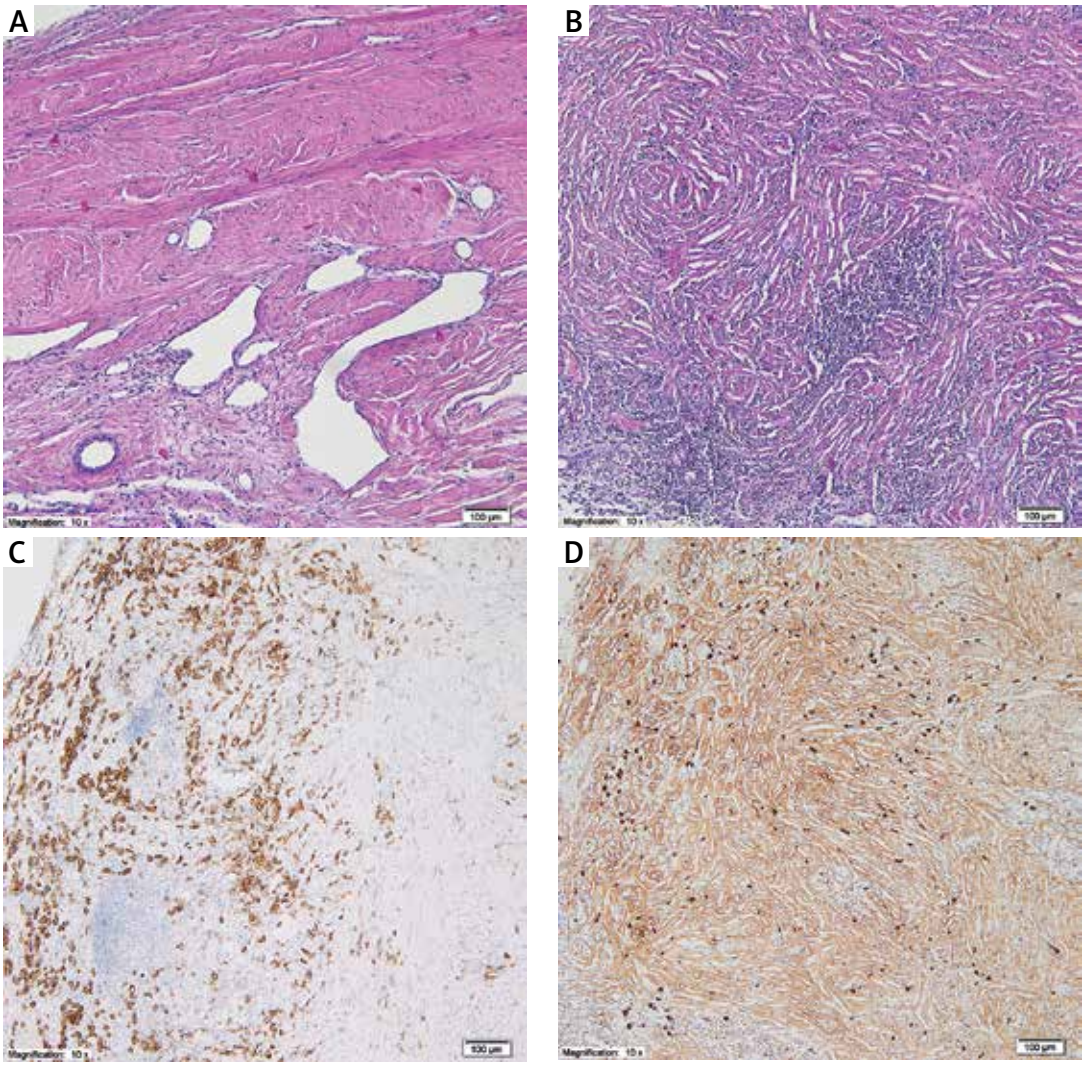

Fig. 3. Histological and immunohistochemical stainings of dura sections. **A**) A section of the dura mater during immunosuppressive treatment, with dilated blood vessels and no inflammatory infiltration found (H&E). **B**) Inflammatory infiltration of the dura consisting mainly of plasma cells (> 30 plasma cells/1 HPF) with fibrosis and hyalinization of the dura (H&E). **C**) CD138 immunohistochemical staining showing an inflammatory infiltrate composed of plasma cells. **D**) IgG4 immunohistochemical staining in inflammatory cells.

showing co-localization of complement deposits and IgG4 in patients with certain autoimmune diseases, but a recent study showed that noticeable CP activation by IgG4 is possible only at very high antigen and antibody concentrations [14]. Instead, we have evidence of the systemic alternative complement pathway (AP) activation, as elevated levels of Bb marker were noticed. AP is constantly active at a low level due to the so-called spontaneous tick-over of the C3 component [12]. Further propagation of this pathway is facilitated on foreign surfaces devoid of complement inhibitors and, conversely, strictly controlled on self surfaces. Such control could be affected in our patient, who carries two genetic variants of soluble complement inhibitors that impair their specific functions: FH p. H402Y [8] in heterozygosis and FI p.T300A [9] in homozygosis. Next to these substitutions, the patients carries six other missense variants of unknown significance located in complement genes, most of them in a homozygous state (Table I). It is highly possible that some or all of them contributed to an unfavourable complotype – the inherited set of variants responsible for a large aggregated

effect that impacts susceptibility to disease [15]. Since the complement is a complex network of protein-protein interactions, a change in a single component may be of a low physiological relevance, but a certain combination can markedly influence the homeostatic balance. In this context, the homozygous mutation in the CFHR4 gene looks interesting. This complement protein has a unique capacity to serve as a platform for stable binding of C3b, factor B, and properdin and thereby forms the AP convertase that is more resistant to decay by FH than the "canonical" C3bBb complex. The convertase-assembling activity is mapped to the first three SCR/CCP domains of CFHR4, a region that contains the homozygous mutation [7]. However, there are no functional studies available for the aforementioned genetic variants so far, and, given that *in silico* prediction tools often fail for complement proteins [6], any statements about the phenotype are problematic. We detected anti-FH antibodies prior to eculizumab administration, but they disappeared during eculizumab treatment and did not rebound after discontinuation when the patient's status worsened, so their role in the pathomechanism is uncertain.

To sum up, we postulate that complement dysregulation may coexist with neurological symptoms in the course of immune-mediated diseases and markedly contribute to an unfavourable clinical picture. Temporal inhibition of the complement system may be considered as a symptomatic treatment of such atypical pathologies that lead to patient stabilization that gains time for a physician to find a proper diagnosis.

Statements and declarations

Ethics approval and patient's consent: Ethics approval was not applicable as the procedures were considered a part of treatment and diagnosis, and not medical experiment. The patient gave written informed consent for the medical procedures described in the article. The patient signed voluntary, written informed consent for publication.

Disclosure

The authors report no conflict of interest.

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