The Turkish Journal of Pediatrics 2022; 64: 787-794
https://doi.org/10.24953/turkjped.2021.1405

Case Report

Optic neuritis in CD59 deficiency: an extremely rare presentation

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ABSTRACT

Background. CD59 is the principal cell inhibitor of complement membrane attack on cells. Stroke, peripheral neuropathy, and recurrent central nervous system attacks have been reported in patients with inherited CD59 deficiency. In this paper, we report a patient with CD59 deficiency associated with two attacks of demyelinating peripheral neuropathy and the third attack as an isolated optic neuritis.

Case. An 8-month-old girl whose sibling died at 12th month of age with recurrent weakness episodes responsive to intravenous immune globulin treatment, presented with weakness in legs and poor sucking. Weakness episodes with neurogenic electromyography suggested CD59 deficiency. Immunophenotypic analysis with flow cytometry showed CD59 deficiency. Sanger sequencing of CD59 gene revealed a homozygous *c146delA* (p.Asp49Valfs*32) mutation. First two attacks were treated with intravenous immunoglobulin therapy without any sequalae. Third attack was an isolated optic neuritis which could not be explained by any other entity. The patient had no response to intravenous immunoglobulin but benefited from pulse steroid therapy. Eculizumab was started every two weeks in order to prevent possible advanced attacks and to reduce their severity.

Conclusion. Although it is a rarely reported disease, better recognition of CD59 deficiency by pediatric neurologists is necessary because it is curable. In addition to different presentations reported, optic neuritis may also be a manifestation of CD59 deficiency.

Key words: complement inhibition, immune dysregulation, demyelinating, eculizumab, optic neuritis.

The complement system (CS) is responsible for recognition and neutralization of bacteria and starting phagocytosis through opsonization. Once complement system is activated, the formation of C3 convertase complexes leads to cleave C3 into two subunits, C3a and C3b. The latter is essential for C5 convertase activity to cleave C5 to C5a and C5b. Freshly activated C5b starts the formation of membrane attack complex (MAC), which is tightly regulated by CD59 through inhibiting recruitment of C9, thereby keeping the cell lysis under control.[1] The relationship between C5 and both the central and peripheral nervous system demyelinating diseases has been shown in many studies.[2-4]

Optic neuritis (ON), an inflammatory condition of the optic nerve causing visual impairment, which can occur as an isolated, monophasic condition, also recurs without signs of any other manifestations of chronic demyelinating diseases such as multiple sclerosis (MS), myelin oligodendrocyte glycoprotein antibody (MOG-Ab) associated disease or neuromyelitis optica spectrum disorders (NMOSD).[5]

Stroke, peripheral neuropathy and central nervous system (CNS) demyelinating disorders have been reported in CD59 deficiency.[6-9] CD59 deficiency has been shown to play an important role in the pathogenesis of NMOSD in mice and rats.[10,11] However, to our knowledge, only

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Received 3rd May 2021, revised 27th July 2021, accepted 28th August 2021.

two siblings have been reported to present optic neuritis, which was thought to be due to CD59 deficiency demonstrated in postmortem studies.[12] We report a patient with CD59 deficiency presenting with first two attacks of early-onset demyelinating peripheral neuropathy and third attack as ON.

Case Report

First attack

An 8-month-old girl presented with a three-day history of generalized weakness and poor sucking. The patient was prescribed amoxicillin-clavunic acid treatment for acute upper respiratory tract infection one week prior. The patient was born at term by cesarean section without any complications and had age-appropriate neurodevelopment. Parents were relatives with four children. The first child had recurrent episodes of weakness after febrile episodes which were responsive to intravenous immunoglobulin (IVIg) treatment and died at 12 months of age without a specific diagnosis. The mother's cousin was also under follow-up at another center with a similar disease. The pedigree of the patient is presented in Figure 1. Neurological examination revealed absent deep tendon reflexes (DTR) and decreased muscle strength [Medical Research Council (MRC) grading system: 3/5] of lower extremities, normoactive DTR and decreased muscle strength (MRC: 4/5) of upper extremities and tongue fasciculation. The patient was unable to hold her head. Clinical features in each attack are shown in Table I. Complete blood count, biochemical tests, vitamin B12, creatine kinase, contrast-enhanced brain magnetic resonance imaging (MRI), contrast-enhanced spinal MRI, cerebrospinal fluid (CSF) examination, and extensive metabolic investigations were normal. Table II shows the laboratory and neuroimaging findings in each attack. Nerve conduction studies were normal but needle electromyography revealed diffuse neurogenic changes. With IVIg (1 g/kg/day for -two days) treatment, sucking improved, head control was gained, but weakness in the lower extremities continued. Weakness episodes with neurogenic electromyography findings suggested CD59 deficiency. Immunophenotypic analysis with flow cytometry showed CD59 deficiency. Sanger sequencing revealed a homozygous, pathogenic variant in the CD59 gene (MIM: 107271), NM_203331: *c146delA* (p.Asp49Valfs*32) (rs587777149). The same variant was found in the mother's cousin. No evidence for hemolysis was detected. Eculizumab treatment could not be given because parental consent could not be obtained. Seven days after IVIg treatment, sucking and other motor functions recovered without any sequelae. Treatment options, durations and benefits during attacks are shown in Table III.

Second attack

The patient who did not have any attacks in the following four months and continued to

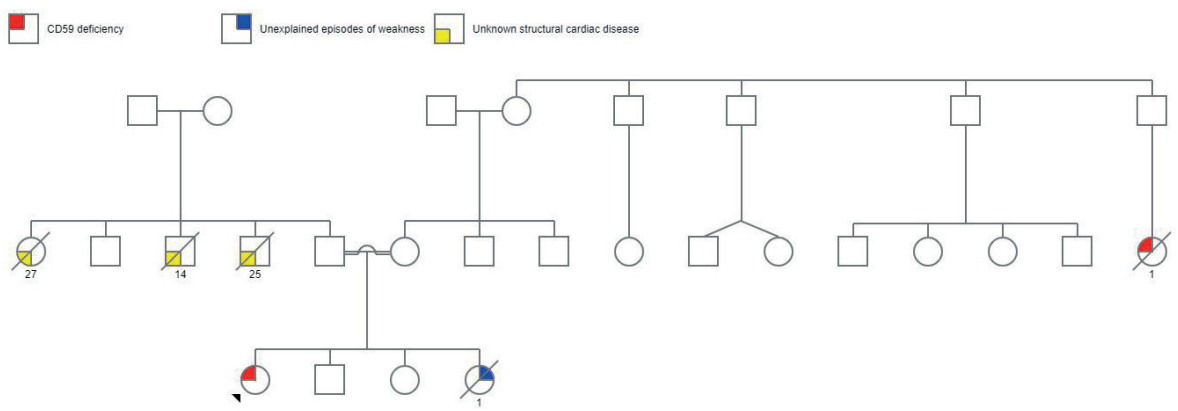

Fig. 1. The pedigree of the patient.

Table I. Clinical features in attacks.

	First attack	Second attack	Third attack
Age (month)	8	12	20
Preceeding febrile infection	(+)	(+)	(-)
Hypotonia	(+)	(+)	(-)
Tongue fasciculation	(+)	(-)	(-)
Optic neuritis	(-)	(-)	(+)
Attack duration before treatment (day)	5	1	1
Attack duration after treatment (day)	7	3	30
Sequelae in muscular system	(-)	(-)	(-)
Sequelae in other systems	(-)	(-)	Optic atrophy

Table II. Laboratory and radiological findings in attacks.

	First attack	Second attack	Third attack
Hemoglobin (g/dL)	12.7	13.4	10.9
Reticulocyte count (%)	NA	1.15	1.41
LDH (U/L)	216	NA	236
Haptoglobin (g/dL)	NA	NA	0.169 (Normal: 0.3-2)
Total bilirubin (mg/dL)	0.7	NA	0.9
Direct Coombs test	(-)	NA	(-)
Peripheral blood smear	No hemolysis	No hemolysis	No hemolysis
Creatine kinase (U/L)	108	81	76
CSF protein (mg/dL)	44.7	NA	29.1
Immunoglobulin index	NA	NA	(-)
MOG-Ab	NA	NA	(-)
AQP4-Ab	NA	NA	(-)
Brain MRI	Normal	NA	Suspicious enhancement in the bilateral olfactory nerves
Spinal MRI	Normal	NA	Normal
Orbital MRI	NA	NA	Increased signal intensity and enhancement in bilateral optic nerves, increased chiasm thickness, heterogeneity in the orbital fatty tissue

CSF: cerebrospinal fluid, MOG-Ab: myelin oligodendrocyte glycoprotein antibody, AQP4-Ab: aquaporin 4 antibody, MRI: magnetic resonance imaging, NA: not available

Table III. Treatment options, dosages, durations and benefits.

	First attack			Second attack			Third attack		
	Duration (day)	Dosage	Benefit	Duration (day)	Dosage	Benefit	Duration (day)	Dosage	Benefit
IVIg	2	1 g/kg/day	(+)	2	1 g/kg/day	(+)	2	1 g/kg/day	(-)
Pulse steroid		NA			NA		10	30 mg/kg/day	(+)
Maintenance steroid		NA			NA			NA	
Eculizumab		NA			NA			Started after the attack	

IVIg: intravenous immunoglobulin, NA: not administered

gain neurodevelopmental milestonesin time, presented with weakness in the legs and poor sucking. The patient had an upper respiratory tract infection 15 days prior and received oseltamivir and clarithromycin treatments. Neurological examination revealed absent DTR in upper and lower extremities, decreased muscle strength of lower and upper extremities (MRC: 3/5). Intravenous immune globulin was given at the same dosage. On the 3rd day, the complaints regressed and the neurological examination findings improved.

Third attack

Despite the advice for close follow-up, the patient was admitted eight months after the second attack, presenting with sudden vision loss and dilated pupils noticed by the mother. Detailed ophthalmological examination revealed loss of light fixation with fixed dilated pupils and no light reflex; however, dilated fundoscopy was normal (Fig. 2). The patient was diagnosed with bilateral ON, since the remainder of the neurological examination and CSF assessment were normal. Orbital MRI showed increased signal intensity on T2 weighted sequences and increased enhancement on contrast enhanced T1 images at the bulbar and retrobulbar level of the bilateral optic nerves **(**Fig. 3A), more prominent on the right, increased thickness of chiasm, heterogeneity in the orbital fatty tissue on the right and suspicious enhancement in the bilateral olfactory nerves (Fig. 3B). Visual evoked potential could not be performed because of patient's poor compliance. Nasopharyngeal swab polymerase chain reaction and serum antibody tests for Coronavirus disease 2019 were negative. Cerebrospinal fluid MOG-Ab and aquaporin 4 antibody (AQP4-Ab) were negative. Rheumatological tests, viral and bacterial serology resulted negative. Pulse steroid (30 mg/kg/day for ten days) and intravenous immunoglobulin (1 g/kg/day for two days) were given without any benefit. After the parental consent, eculizumab treatment was planned biweekly. Routine vaccination scheme and meningococcemia prophylaxis were collocated. Five days after the steroid therapy, the patient was uncomfortable with light and avoided objects while walking. Ophthalmological examination revealed bilateral optic disc pallor with the lack of optokinetic nistagmus (OKN). Subjective complaints about vision disappeared. The neuro-ophthalmological examination revealed bilateral normoisochoric pupils with central, steady, and maintained fixation on the 30th day of the beginning of symptoms (15th day of the end of steroid treatment). Radiologic examination after one month revealed regression of optic and olfactory nerve findings but three new cerebellar demyelinating small lesions on T2 images without clinical correlation (Fig. 3C, Fig. 3D). Considering that meningococcal vaccination would delay optimal treatment, although the second dose of

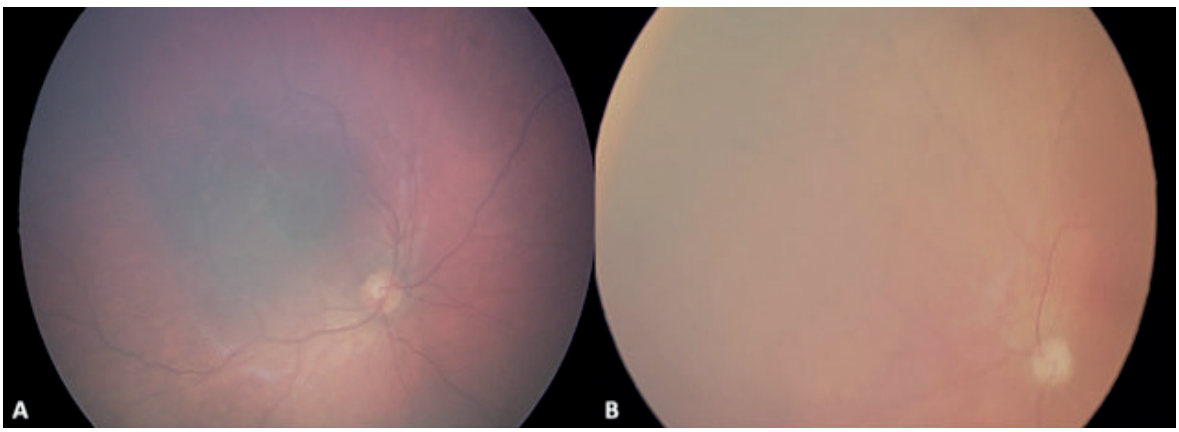

Fig. 2. Dilated fundoscopy revealed normal findings.

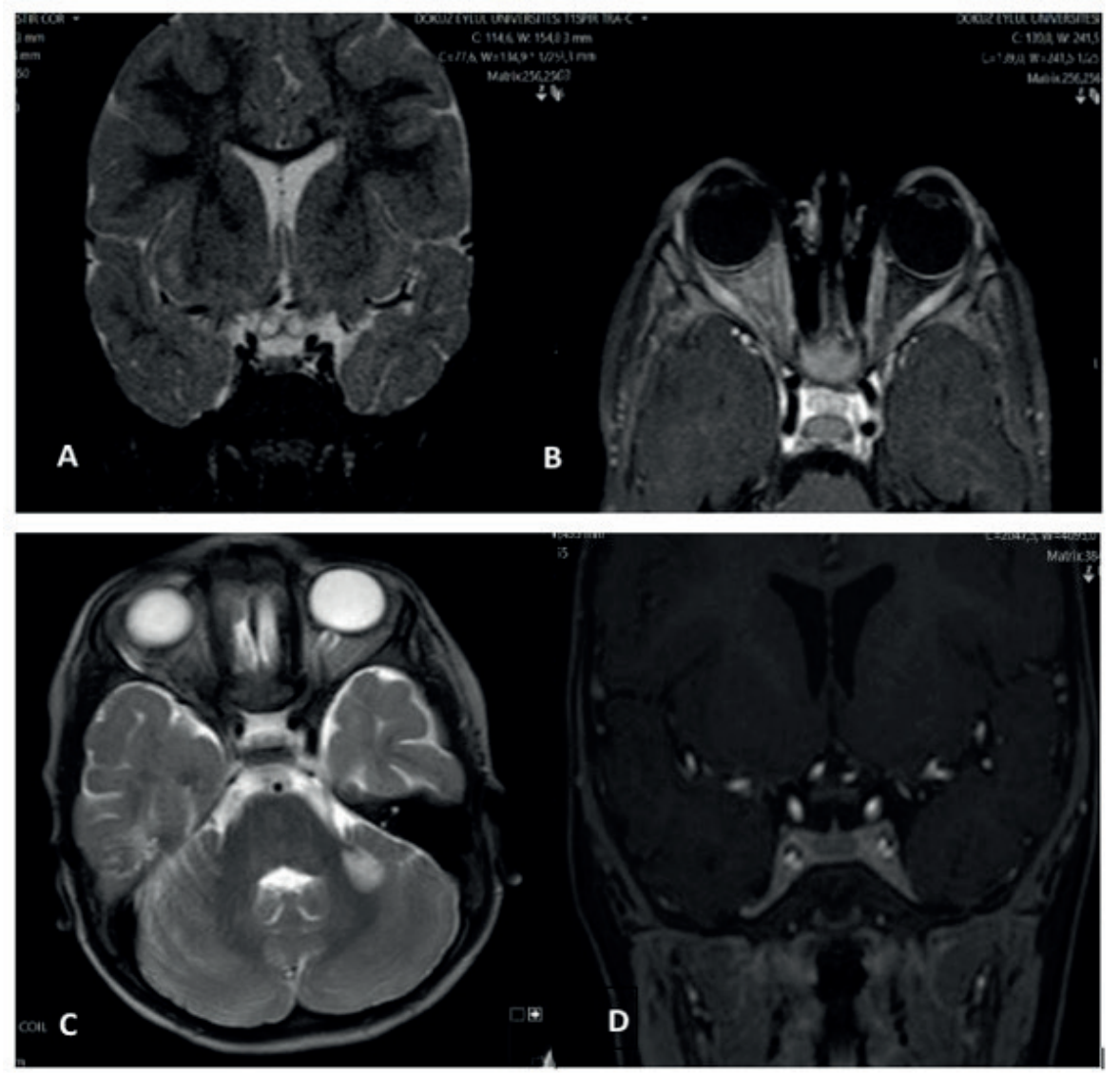

Fig. 3. (A) Retrobulbar optic nerves appearing hyperintense and swollen on coronal T2 weighted sequence. **(B)** Heterogeneity in the orbital fatty tissue on the right and increased enhancement bilateral optic nerves on axial contrast enhanced T1 sequence. **(C)** Cerebellar demyelinating lesion on axial T2 weighted sequence. **(D)** Regression of optic and olfactory nerve enhancement on T1 weighted sequence.

vaccine had not been administered yet, the first dose of eculizumab (300 mg, intravenous) was administered on the 35th day of the symptom onset with penicillin V prophylaxis. Detailed ophthalmological examination performed after the sixth dose of eculizumab treatment revealed positive OKN, bilateral central, steady, and maintained fixation with normoisochoric pupils and positive light reflexes on both eyes; however, dilated fundoscopy depicted bilateral optic atrophy (Fig. 4) Cycloplegic refraction was found as -1.75 diopters (D) of myopia with -3 D of astigmatism in the right eye and -3.5 D of astigmatism in the fellow eye. The patient is still followed-up with no further attacks after eculizumab which is administered biweekly. The parents gave their informed consent for this publication.

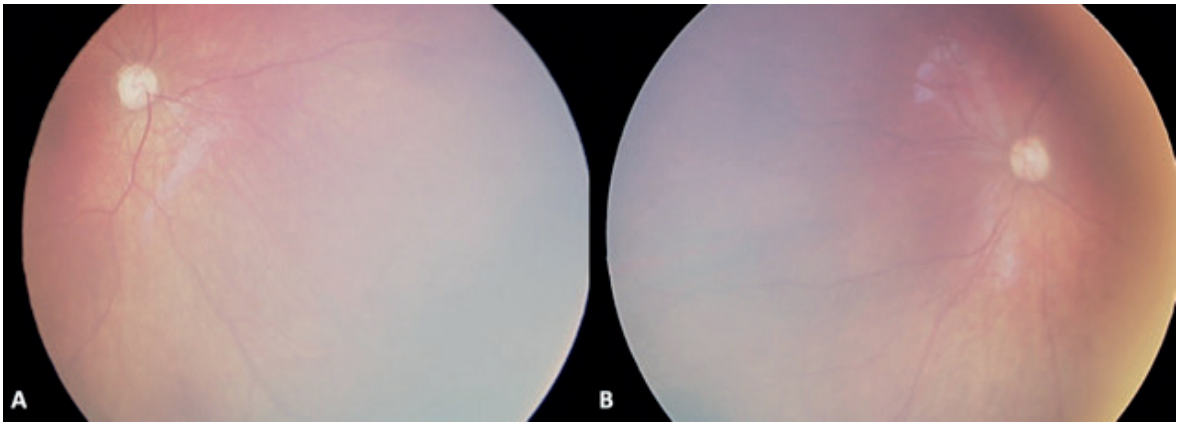

Fig. 4. Bilateral optic atrophy was diagnosed by dilated fundoscopy.

Discussion

As interest in MOG-Ab has increased, there is an increase in pediatric ON studies. Myelin oligodendrocyte glycoprotein antibody was thought to be most commonly associated with acute disseminated encephalomyelitis (ADEM) in children; however, recent studies have shown ON to be the predominant phenotype. Although MOG-Ab was previously thought to identify a benign MS subtype, it appears to be predictive for a non-MS disease and is detected in patients with AQP4-Ab negative NMOSD. Now MOG-Ab associated disease has been reassessed as a distinct entity.[5] Despite all these new antibodies and classifications, CD59 deficiency associated with nervous system involvement has been described in a small number of patients in the literature. CD59 deficiency has been reported to cause Coombs-negative hemolysis, early-onset recurrent peripheral neuropathy, chronic inflammatory demyelinating polyneuropathy, and stroke.[6-8] A homozygous missense mutation, p.Cys89Tyr in CD59 gene was identified in five infants from four unrelated families of North-African Jewish origin with Coombs-negative hemolysis accompanied by sensorimotor, demyelinating, or axonal peripheral polyneuropathy.[13] Based on these results, Ben-Zeev et al.[12] reported two historical unsolved siblings who carried the same mutation and died 17 years before the date of report. The patients were reported to have a similar course but also developed recurrent strokes, bilateral optic atrophy, and retinal involvement as hypopigmented retina and depigmented scar-like retinal lesion in one eye each. While the authors speculated that the pathogenesis of optic nerve damage may be similar to the course of the peripheral neuropathy in CD59 deficiency, macular damage secondary to MAC activation has been proposed as the mechanism of retinal involvement in the fashion of age-related macular degeneration.[14] Apart from this report, CNS involvement is relatively rare in the literature. In two siblings reported from Turkey, one had peripheral neuropathy while the other had ADEM-like presentation.[15] Similarly, a case with isolated recurrent CNS inflammatory disease has been reported.[9]

Besides ON caused by CD59 deficiency were reported in two siblings, an association between CD59 deficiency and NMOSD was also demonstrated in animal models.[10,11] Aquaporin 4 antibody binds to aquaporin 4 channel on astrocytes and activates the classical CS resulting demyelination in NMOSD.[16] Zhang and Verkman[10] showed NMOSD pathology produced by AQP4-Ab and complement following CD59 inactivation in mice. However, a major limitation of mice as models of NMOSD is the almost-zero activity of their classical CS because of complement inhibitory factors in

mice serum. Yao and Verkman[11] showed the role of CD59 deficiency in the NMOSD pathogenesis by using rats and transferring passive AQP4-Ab to models with CD59 deficiency, as they have human-like CS.

Eculizumab is a humanized monoclonal antibody that inhibits the terminal complement protein C5 to prevent its cleavage into C5a, which is proinflammatory, and C5b, which is responsible for the MAC formation.[17] Thereby, eculizumab prevents overactivation of MAC and is used in the treatment of inherited CD59 deficiency and other disorders caused by defective complement regulation, such as paroxysmal nocturnal hemoglobinuria, hemolytic uremic syndrome, and CD55 deficiency.[18] Eculizumab seems to stabilize or improve neurological symptoms and be beneficial for discontinuing other immunomodulating treatments in CD59 deficiency.[19] Eculizumab is the first drug to be approved in the European Union, United States of America, Canada and Japan specifically for use in adults with AQP4-Ab seropositive NMOSD.[17] Even though demyelinating polyneuropathy attacks were partially responsive to high dose steroids and IVIg in the patients reported by Ben-Zeev et al.[12], the effects of these treatments on optic atrophy or retinal involvement were not mentioned. Although eculizumab was not used in these patients, the authors suggested that eculizumab is necessary to prevent multisystem involvement in patients with CD59 deficiency.[12] We suggest that eculizumab can also prevent possible future attacks or reduce their severity in our patient.

CD59 deficiency may be a relatively common autosomal recessive disease in Turkey. Child neurologists should know classical findings of the disease because the attacks are preventable with eculizumab. Optic neuropathy may be a manifestation of CD59 deficiency.

Ethical approval

The parents gave their informed consent for this publication.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: CG, EY, EY, ASHK, GSU, TO, AY, UY; data collection: CG, EY, EY, ASHK, GSU, TO, AY, UY; analysis and interpretation of results: CG, UY, draft manuscript preparation: CG. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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