Post-malaria neurological syndrome: a rare neurological complication of malaria

Sanjay K. Yadava1 · Ashley Laleker1 · Tasaduq Fazili1

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Abstract

Background Post-malaria neurological syndrome (PMNS) is a rare self-limiting neurological complication that can occur after recovery from malaria, usually severe falciparum malaria. It is characterized by a myriad of neuropsychiatric manifestations including mild neurological deficit to severe encephalopathy. PMNS was first described in 1996 and since then there have been 48 cases reported in the English literature. We report another case of PMNS in a 24-year-old healthy male and present a review of the disease entity.

Method We searched PMNS-related journal articles and case reports in the English literature, using PubMed and Google search engines. A total of forty-nine cases meeting the diagnostic criteria of PMNS were selected in this review.

Conclusion PMNS is a rare complication of severe malaria that might be underreported. It can develop up to 2 months after clearance of parasitemia. Clinical features can be variable. Most cases are self-limited, but more severe cases may benefit from steroid therapy.

Keywords Post-malaria neurological syndrome (PMNS) · Falciparum malaria

Case history

A 24-year male presented with fever, confusion, dysarthria and grand mal seizure. He was recently diagnosed with severe falciparum malaria with multi-organ dysfunction, after being non-compliant with anti-malarial prophylaxis, while working for the Peace Corps in Togo in November 2017. He was treated with IV quinine with complete clearance of his parasitemia. He fully recovered but still required dialysis, and returned to the United States in December 2017. On the day of admission in late December, he arrived for scheduled dialysis and was found to be tachycardic which prompted him to be sent to an outside hospital, where he had an episode of confusion and dysarthria, after which he returned to his baseline mentation. A computed tomography (CT) scan of the head was unremarkable. Next day, the patient had a grand mal seizure. A CT of the head was repeated which was again negative for any acute findings. No focal neurological deficit was observed following the seizure. However, the patient remained lethargic, agitated, and was not speaking or following commands, prompting the transfer to our hospital. On arrival, had a fever of 38.9 °C with sinus tachycardia of 130 beats/min, normal blood pressure and Glasgow Coma Scale (GCS) score of 7. He was lethargic, wincing with sternal rub, not responding to verbal commands, and had no meningismus.

The patient’s white count was 15.3 × 10³/µL (4–10 × 10³/µL), hematocrit of 27.5%, with normal platelets (286 × 10³/µL). His creatinine was 2.11 mg/dL, sodium 135 mmol/L, potassium 3.9 mmol/L and serum glucose 97 mg/dL. The total bilirubin and liver enzymes were normal. His human immunodeficiency virus, Epstein–Barr virus, dengue, West Nile virus and Lyme serology were negative, and rapid plasma regain (RPR) was non-reactive. Cerebral fluid (CSF) analysis revealed WBC of 75/µL with 91% lymphocytes, elevated protein of 65 mg/dL and glucose of 64 mg/dL. The total bilirubin and liver enzymes were normal. His human immunodeficiency virus, Epstein–Barr virus, dengue, West Nile virus and Lyme serology were negative, and rapid plasma regain (RPR) was non-reactive. Cerebral fluid (CSF) analysis revealed WBC of 75/µL with 91% lymphocytes, elevated protein of 65 mg/dL and glucose of 64 mg/dL. CSF Gram’s and acid-fast bacillus stains were negative. CSF polymerase chain reaction (PCR) pathogen panel (Biofire) for

Sanjay K. Yadava
yadavas@upstate.edu

1 Department of Medicine, Division of Infectious Disease, SUNY Upstate Medical Center, Syracuse, NY, USA

1 CSF pathology panel (Biofire) includes E. coli K1, H. influenza, Listeria monocytogenes, N. meningitides, Streptococcus agalactiae, Streptococcus pneumoniae, Cytomegalovirus, Enterovirus, herpes simplex viruses 1 and 2, human herpes virus 6, human Parechovirus, varicella zoster virus, Cryptococcus neoformans/gattii.
neurotropic bacteria, fungi and viruses was negative. CSF, blood, urine cultures and toxicology screening test were negative as well. CSF VDRL, Cryptococcal antigen and respiratory viral panel (RSV) were negative. Malaria smears were done on admission and the next day, and both were negative.

Chest X-ray, CT head and CT abdomen and thorax were unrevealing. Magnetic resonance imaging (MRI) of the brain revealed nonspecific focus of signal abnormality in the posterior limb of the right internal capsule without evidence of acute infarction in this region.

The patient was started on broad-spectrum antibiotics, acyclovir and Artemether–Lumefantrine, which were subsequently discontinued following negative laboratory results. A clinical diagnosis of PMNS was made and prednisone therapy was started at 1 mg/kg/day. His mentation began improving the next day, and steroids were tapered over 5 days with full recovery. Subsequent follow-up at 3 months revealed normal neurological examination.

**Discussion**

There are several neurological syndromes that can occur following complete recovery from malaria, in particular *Plasmodium falciparum*. These syndromes include PMNS, delayed cerebellar ataxia (DCA), acute inflammatory demyelinating polyneuropathy (AIDP) and acute disseminated encephalomyelitis (ADEM) [1–3]. PMNS shares many characteristics of ADEM; hence, some authors describe PMNS as a form of ADEM.

PMNS is a predominantly self-limited condition, which can occur following severe falciparum malaria, not necessarily cerebral [1, 3]. Schnorf et al. [4] classified the syndrome into three categories based on clinical severity: a mild form characterized by isolated cerebellar ataxia or postural tremor; a diffuse, relatively mild encephalopathic form, associated with acute confusion or seizures; and a severe encephalopathy typified by motor aphasia, generalized myoclonus, postural tremor, and cerebellar ataxia.

The incidence of PMNS in patients after falciparum malaria can range from 0.7 to 1.8 per 1000 and it is 300 times more common in patients with severe rather than uncomplicated malaria [1]. The diagnosis of PMNS requires both proven symptomatic malaria infection with full initial clinical recovery and clearance of parasitemia following treatment, and the development of neurological or psychiatric symptoms within 2 months of acute illness [1].

We searched PMNS-related articles using PubMed and Google search engines and a total of forty nine cases, including our case, met the diagnostic criteria (Table 1). 24 (49%) infections were contracted in Asia, 24 (49%) in Africa, and 1(2%) in the Dominican Republic. Although most cases of *P. falciparum* occur in Africa, our results appear to be skewed by the large Vietnamese study [1]. There were 36 males and 13 females with male:female ratio of around 2.76:1. All the cases were preceded by falciparum malaria except one, which had *P. vivax*, reported from India. PMNS occurred mostly in patients who had preceding severe falciparum malaria. The mean parasitemia was 19.4% for 22 cases in which it was quantified. The common clinical features were confusion (50%), fever (47.7%), seizure (31.8%), speech abnormalities (18.2%), tremor (18.2%), behavioral abnormalities (16%), impaired consciousness (16%), myoclonus (11.3%), ataxia (11.3%) and headache (6.8%). Less common features were psychosis (6.8%), catatonia (4.5%), hallucinations (6.8%), weakness (4.5%), dizziness (4.5%), mydriasis (4.5%), nystagmus (2.2%), paraplegia (2.2%), and somnolence (2.2%).

The median duration of onset of PMNS in Nguyen’s study of 22 patients was 4 days; in 22 patients (out of 27 that these data were available for) the median duration was 14 days. However, the syndrome can occur anywhere from 0 to 60 days following clearance of parasitemia [1]. The median duration of symptoms was 13 days (range 3–25 days) excluding Nguyen’s study; in his study, it was 2.5 days (range 1–10).

The exact pathogenesis of PMNS is not known. Some authors suggest obstruction of cerebral microvasculature by parasitized red blood cell inducing cerebral hypoxemia [1, 7]. Hsieh et al. [7] described brain single-photon emission computed tomography (SPECT) findings with markedly decreased radioactivity. However, this mechanism is questionable as obstruction of microvasculature does not seem plausible due to the potentially long delay between malaria episode and PMNS. Another postulated hypothesis is immune mediated based on a positive response to corticosteroid therapy in some patients, and lagging of onset of PMNS symptoms after resolution of malaria symptoms [4]. An increment of serum and CSF concentrations of inflammatory cytokines such as TNF-alpha, IL 2 and IL 6 has been described in some cases of delayed post-malaria cerebellar syndrome, which decreased following steroid therapy [24]. There is also some evidence of possible molecular mimicry, whereby antibodies to antigens expressed by certain strains of *P. falciparum* cross-react with antigens in the CNS [5]. However, a study by Siriez et al. [22] was unable to detect intrathecal IgG and specific *P. falciparum* antibodies in the CSF. Coinfection or reactivation of a viral infection capable of causing encephalitis...
Table 1 Summary of PMNS cases reported in the literature

| No. | Author         | Location  | Age (year)/sex | P. falciparum parasitemia (%) | Onset of PMNS (days) | Signs and symptoms                                                                 | Anti-malarial treatment | Laboratory findings during PMNS | Steroid use | PMNS duration and clinical evolution |
|-----|----------------|-----------|----------------|-----------------------------|----------------------|-----------------------------------------------------------------------------------|-------------------------|----------------------------------|-------------|-------------------------------------|
| 1–22| Nguyen et al.  | Vietnam   | Mean age 29 M—15 F—7 | NA                          | Median 4 Range 0–60  | Fever (9), acute confusion (15) generalized seizures (8), fine tremor (1) catatonia with waxy flexibility (2) psychosis (3) | Artemisinins (13), quinine (10), sulfadiazine (4), Mefloquine (17) | Elevated O.P. 1/22 WBC 8–80 8/22 lymphocyte predominance 8/8; elevated protein 13/22 | No          | Median = 2.5 (range 1–10)            |
| 23  | Schnorf et al. | Africa 1998 | 34/F           | 45%                         | 17                   | Tremor, word-finding difficulty, expressive aphasia, mild cerebellar ataxia, tonic–clonic seizures, fever, myoclonus | Quinine, clindamycin | WBC 10/uL, 95% lymphs; protein 0.6 g/L | Abnormal/normal | IV MP 100 mg × 3 days with tapering for 10 days | Fast improvement after 24 h of initiation of steroid. All the symptoms resolved by 10 days except postural tremor of arms |
| 24  | Schnorf et al. | Cameroon 1998 | 61/M           | 50%                         | 16                   | Word-finding difficulty, expressive aphasia headache, irritability myoclonus, tremor, fever, ataxia | Quinine, doxycycline, Mefloquine | WBC 80/uL, 87% lymphs, 12% mono; protein 1.8 g/L | Normal/normal | Prednisone 60 mg for 4 days | Rapid improvement of all symptoms after 24 h of initiation of steroid. All symptoms resolved by 13 days with residual postural tremor of arms |
| 25  | Mohsen et al.  | Kenya 2000 | 30/F           | 29%                         | 35                   | Confusion, lethargy, language difficulties prosopagnosia, seizure, odd behavior | Quinine doxycycline | WBC 22 lymphs/uL, protein 1.4 g/L | Abnormal/normal | No | Gradual improvement of symptoms over a week and recover to normal in 14 days |

PMNS: Post-malaria neurological syndrome
CSF: Cerebrospinal fluid
MRI/CT: Magnetic resonance imaging/computed tomography
| No. | Author          | Location | Age (year)/sex | P. falciparum parasitemia (%) | Onset of PMNS (days) | Signs and symptoms | Anti-malarial treatment | Laboratory findings during PMNS | Steroid use | PMNS duration and clinical evolution |
|-----|----------------|----------|----------------|-------------------------------|----------------------|--------------------|-----------------------|---------------------------------|-------------|-------------------------------------|
| 26  | Lawn et al. [7] | Gambia 2002 | 44/M           | 32%                           | 14                   | Fever, incoherent speech, confusion | Quinine, S/P | 4 lymphs/ul, protein 0.89 g/L | Normal/normal          | No          | Steady improvement of confusional state over a week. The total PMNS duration was 15 days |
| 27  | Lawn et al. [5] | Gambia 2002 | 22/F           | 22%                           | 7                    | B/L UE and LE postural tremor nominal aphasia fever | Quinine, S/P | 59 lymphs/ul, protein 2.59 g/L | Normal/normal          | Prednisone 60 mg/day with tapering over 10 days | Rapid diminution of all symptoms after initiation of steroid. All symptoms resolved by 5 days of treatment. PMNS duration was 17 days |
| 28  | Falchook et al. [6] | Ghana 2003 | 50/F           | 0.2%                          | 11                   | AMA, GCS 10, UE and LE myoclonus jerking, tremors visual/auditory hallucinations expressive aphasia | Quinine, doxycycline, malarone | 3WBC/ul, protein 0.31 g/L | Abnormal/normal          | No          | 10 days after the onset of symptoms, her mental status began to improve and all neurological symptoms resolved over 2 days. PMNS duration was 12 days |
| No. | Author     | Location       | Age (year)/sex | P. falciparum parasitemia (%) | Onset of PMNS (days) | Signs and symptoms | Anti-malarial treatment | Laboratory findings during PMNS | Steroid use | PMNS duration and clinical evolution |
|-----|------------|----------------|----------------|-------------------------------|----------------------|--------------------|-----------------------|--------------------------------|-------------|-------------------------------------|
| 29  | Hsieh et al. [7] | Malawi 2003    | 50/M           | NA                            | 14                   | Dizziness, headache, horizontal diplopia, mild hand tremor, unsteady gait and easy falling | Augmentin, Cipro, clindamycin, ceftriaxone, artesunate, doxy, quinine, Mefloquine | WBC-0/mL3; glucose, 50 mg/dL; protein, 205 mg/dL | Normal/NA | IV MP 80 mg/day x 3 days f/b PO prednisone 45 mg/day x 6 days |
|     |            |                |                |                               |                      |                    |                       |                                |             | Unsteady gait persisted for 2 wks until initiation of steroids which gradually improved. He absconded on the 9th day of steroids t/t with clear consciousness and ambulation |
| 30  | Palmieri et al. [8] | Mozambique 2004 | 42/M           | > 10%                         | 14                   | Nominal aphasia, fine tremor (intention) fever, confusion, GCS 12 | Quinine | 45 lymphs/ul, protein 1.29 g/L | Normal/normal | No | Neurological symptoms improved steadily over a week. No residual neurological sequelae. PMNS duration was 9 days |
| 31  | Zambito et al. [9] | French Guinea 2004 | 60/M           | 0.02%                         | 9                    | Generalized weakness disorientation tremor, dizziness | Quinine, doxy, ceftriaxone | 20 lymphs/ul, protein 2.52 g/L | Normal/normal | No | Symptoms resolved spontaneously over 3 days |
| 32  | Silva-pinto et al. [10] | Angola 2004    | 38/M           | 70%                           | 11                   | Headache, behavior impairment, ataxic gait, consciousness impairment/AMA | Quinine/doxy-cycline | 75 mononuclear protein 1.14 g/L glucose (% CSF/Serum) 60 | Abnormal/NA | IV MP 1 g/day x 3 days | Gradual improvement, recovery to normal status in 10 months |
Table 1 (continued)

| No. | Author                  | Location   | Age (year)/sex | \(P. falciparum\) parasitemia (\%) | Onset of PMNS (days) | Signs and symptoms                                      | Anti-malarial treatment | Laboratory findings during PMNS | Steroid use | PMNS duration and clinical evolution |
|-----|-------------------------|------------|----------------|------------------------------------|----------------------|--------------------------------------------------------|-------------------------|----------------------------------|-------------|-------------------------------------|
| 33  | van der Wal et al. [11] | Kenya 2005 | 53/M           | 6%                                 | 17                   | Mixed aphasia, confusion, position tremor, mydriasis, generalized, restlessness, fever word-finding, difficulty | Quinine, ciprofloxacin, cefazolin | WBC 5/uL, 24% lymphs; protein 0.67 g/L | Prednisone 75 mg x 3 days then tapered with 10 mg/day | Rapid recovery seen within 24 h of initiating steroid. PMNS duration was 12 days |
| 34  | Mizuno et al. [12]      | West Africa 2005 | 54/M          | 10%                                | 21                   | Incoherent speech acute confusion fever, unco-operative behavior | Mefloquine, artemisinin | 10 lymphs/ul, protein 0.83 g/L | No | Acute confusional state improved steadily over a week and full recovery without sequelae by 13th day |
| 35  | Prendki et al. [13]     | Ivory Coast 2006 | 19/M          | 2.5%                               | 57                   | Dizziness, mood disorders, generalized seizures, fever, GCS 6 | Quinine | 76 WBC/ul, 100% lymphs protein 0.52 g/L | No | Improved gradually over 14 days with no neurological sequelae |
| 36  | Prendki et al. [13]     | Gambia 2006  | 17/M           | 9%                                 | 14                   | Fever, confusion, clouded consciousness/AMA, generalized seizure | Quinine | 26 WBC/ul, 91% lymphs; protein 1.88 g/L | No | Improved gradually over 12 days with no neurological sequelae |
Table 1 (continued)

| No. | Author          | Location          | Age (year)/sex | *P. falciparum* parasitemia (%) | Onset of PMNS (days) | Signs and symptoms                                                                 | Anti-malarial treatment | Laboratory findings during PMNS | Steroid use | PMNS duration and clinical evolution |
|-----|-----------------|-------------------|----------------|---------------------------------|----------------------|-----------------------------------------------------------------------------------|------------------------|----------------------------------|-------------|-------------------------------------|
| 37  | Markley et al.  | Dominican Republic | 43/M           | 23%                             | 18                   | Headache, tremor, word-finding difficulty, disorientation, inattention, acalculia, agnaphesia, conductive aphasia, perseveration | Mefloquine, quinine, doxycycline, A/P | 20 lymphs/ul, protein 0.92 g/L | Prednisone 60 mg/day with tapered over 1 week | Improved dramatically over 3 days after initiation of steroid and all symptoms resolved by 5th day except a mild tremor. 21 days |
| 38  | Matias et al.   | India             | 61/M           | 50%                             | 2                    | Delirium, somnolence, dysarthria, dysphagia, cerebellar ataxia, nystagmus, palatal palsy | Quinine, doxycycline | 4WBC/ul, protein 1.38 g/L | Methylprednisolone 1 g/day × 3 days | Significant improvement of neurological deficits with steroid. All symptoms resolved except mild dysarthria and ataxia by 25th day. Normal NE by 9 months |
| 39  | Odawara et al.  | Sierra Leone, 2009| 56/M           | 4.8%                            | 17                   | Fever, ataxia, tremor, confusion | Mefloquine/artesunate | 19 WBC, protein 1.43 g/L | No | Gradually improved without specific treatment and without residual symptoms in 20 days |
| 40  | Rakotovivelo et al. | Madagascar   | 16/M           | 0.87%                           | 9                    | Confusion and tremor, ataxia, seizure | Quinine, artesunate and amodiaquine | 31 WBC with 98% lymphocytes, 2 g/L protein | No | Resolution of all neurological symptoms in 10 days |
| No. | Author               | Location          | Age (year)/sex | P. falciparum parasitemia (%) | Onset of PMNS (days) | Signs and symptoms                                                                 | Anti-malarial treatment | Laboratory findings during PMNS (CSF/CT) | Steroid use | PMNS duration and clinical evolution |
|-----|----------------------|-------------------|----------------|-------------------------------|---------------------|-------------------------------------------------------------------------------------|-------------------------|------------------------------------------|-------------|-------------------------------------|
| 41  | Pace et al. [18]     | Sierra Leone 2011 | 48/F           | NR                           | 10                  | Nystagmus, minimal neck and shoulder muscle weakness with hyperreflexia, flaccid paraplegia with retained reflexes, urinary retention, reduced anal tone and a sensory loss | Artesunate and amodiaquine | NP Abnormal/NA MP × 3 days | Abnormal/NA | Neurological deficit began improving within 36 h of steroid with minimal paraparesis by 2 weeks. 14 days |
| 42  | Mittal et al. [19]   | India 2015        | 60/M           | plasmodium vivax              | 7                   | Seizure, cognitive dysfunction tremors, mild aphasia and inappropriate response to command, weakness | NA                      | NP Abnormal/NA No                 | Abnormal/NA | No                                  |
| 43  | Silva-pinto et al. [10]| Ivory coast, 2016| 45/M           | 25%                          | 11                  | Fever, behavior impairment, myoclonus, visual hallucination, decrease consciousness/AMA, working memory deficit | Quinine/doxycycline 99 monocyte, 2.09 g/L glucose (%, CSF/Serum) 70 | Normal/NA No                           | Gradual improvement with mild cognitive dysfunction after 6 months |
| No. | Author | Location     | Age (year)/sex | P. falciparum parasitemia (%) | Onset of PMNS (days) | Signs and symptoms                                                                 | Anti-malarial treatment | Laboratory findings during PMNS | Steroid use | PMNS duration and clinical evolution |
|-----|--------|--------------|----------------|------------------------------|---------------------|----------------------------------------------------------------------------------|------------------------|---------------------------------|-------------|-------------------------------------|
| 44  | Costa et al. [20] | Angola, 2016 | 57/M           | 8%                           | 11                  | Fever, behavior impairment, myoclonus, circadian rhythm disturbance, working memory deficit, visual construction inability | Quinine/doxycycline   | 159 monocyte, 2.12 g/L, glucose (%CSF/serum)60 | Abnormal/NA | MP 5days | Fast improvement persistence of slight attention deficit |
| 45  | O’Brien et al. [2] | West Africa, 2016 | 42/M           | 5.6%                         | 30                  | Confusion, disorientation, memory and communication difficulties                  | Quinine/doxycycline   | Abnormal/NA | MP×3 days followed by prednisone 60 mg, tapering over 6 weeks | Slowly improved clinically and after 16 days had significant improvement except some cognitive, memory and communication problem. All symptoms completely resolved by 5–6 months |
| 46  | Chiabi et al. [21] | Cameroon     | 7/F            | NR                           | 1                   | Visual hallucinations, confusion, incomprensible words, behavioral impairment      | Artesunate             | NP                            | NP          | No                          | Symptoms started regressing after 48 h and all symptoms resolved by day 3 |
| 47  | Siriez et al. [22] | Mali, 2017   | 14/M           | 9%                           | 10                  | Impaired consciousness/AMA, mydriasis                                           | Quinine, A/P           | 35 WBC with 100%monocytes, protein 1.22 g/L | Normal/normal | No | Neurological signs resolved fully within 48 h |
has been suggested as another possible mechanism [4]. Schnorf et al. found elevated IgG and IgM antibodies against CMV and EBV in the serum but not the CSF of one of his patients, and positive IgG antibody against varicella zoster virus in the CSF and serum of the same patient albeit PCR repeatedly failed to detect genetic material of EBV, CMV, and VZV in the CSF. In fact, *P. falciparum* infection has been shown to induce polyclonal B cell activation and subsequent secretion of different antibodies, causing false-positive serological tests [25, 26]. Nguyen et al. implicated Mefloquine as a possible cause of PMNS since 17 of 22 patients (77%) were treated with Mefloquine. However, altogether 25 of 46 PMNS cases (54.3%) in our review were not taking Mefloquine.

CSF findings in PMS may be variable and may show risen opening pressure, pleocytosis and elevated protein. CSF analysis was performed in all cases except two, which revealed lymphocytic pleocytosis in two-thirds of the patients with an elevated protein in one-third.

MRI brain can be unremarkable or reveal some signal changes in various parts of brain. 10 out of 23 cases had abnormal MRI of brain. The abnormalities consisted of nonspecific findings with increased signal uptake in various regions of brain, including the periventricular areas, brain stem, thalamus, corona radiata, internal capsule, and cerebellum. In one case, there was inflammation of spinal cord along with brain stem and cerebellar peduncles while another patient had evidence of optic neuritis with cerebral edema [18, 23]. CT scans were normal in all cases in which MRI was abnormal.

PMNS usually does not require specific treatment. However, in severe cases steroids may help to hasten recovery [4, 7, 14]. Schnorf et al. observed two patients that continued to have worsening neurological symptoms until steroids were initiated, with rapid recovery [4]. Similarly, Hsieh et al. described persistent unsteadiness in their patient with PMNS for 2 weeks until the use of corticosteroids, which resulted in dramatic recovery. Overall in our literature review, 12 out of 48 were treated with steroids and all had rapid recovery within a few days of initiation of steroid therapy except two patients in which recovery was gradual. About half of the patients received oral prednisone initiated at 1 mg/kg/day and tapered over 7–10 days while most of the remaining patients received IV methyl prednisolone for 3–5 days. The neurological signs and symptoms of PMNS in most of patients resolved within days to weeks.

In conclusion, PMNS is a rare complication of severe malaria that might be underreported. It can develop up to 2 months after clearance of parasitemia. Clinical features can be variable. Most cases are self-limited but more severe cases may benefit from steroid therapy. In patients with recent history of malaria that present with neuropsychiatric symptoms, PMNS should be strongly considered.
Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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