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Case Report: An Adolescent Girl with Isolated Neuropsychiatric Features and Apparent Post-Malaria Neurological Syndrome

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Abstract. The post-malaria neurological syndrome (PMNS) is an unusual and relatively underreported complication of malaria, which usually occurs after the resolution of acute febrile illness and the patient is free from parasitemia. The clinical spectrum of the PMNS varies from acute-onset cerebellar ataxia to significant encephalopathy with focal deficits resembling acute disseminated encephalomyelitis. Uncommon presentations of PMNS include Guillain–Barre syndrome, postural tremor, or even isolated neuropsychiatric features. Although in a significant proportion of PMNS cases clinical resolution occurs with conservative treatment only, corticosteroids have been used in an attempt to hasten recoveries. Here, we present a case of a 12-year-old girl with acute onset, isolated neuropsychiatric features, following *Plasmodium falciparum* malaria. Neuroimaging, clinical examination, and cerebrospinal fluid studies were within normal limits. The child recovered completely after treatment with methylprednisolone pulse therapy. This case report illustrates the need for creating awareness about this uncommon complication of malaria. In view of the uncommon complication, early diagnosis and prompt treatment might help in the early resolution of symptoms.

INTRODUCTION

Post-malaria neurological syndrome (PMNS) is a relatively rare complication, and it usually occurs after the acute febrile illness has resolved and the patient is free from parasitemia.[1] The clinical spectrum of the PMNS varies from acute-onset cerebellar ataxia to significant encephalopathy with focal deficits resembling acute disseminated encephalomyelitis (ADEM).[1] Another manifestation can be acute-onset axonal or demyelinating polyneuropathy resembling Guillain–Barre syndrome, postural tremor, confusion, or neuropsychiatric features.[2,3] Although few case series and case reports from across the globe have reported PMNS in adults, pediatric data regarding this rare entity in the literature is very scarce.[3]

In most of the cases, the diagnosis of the PMNS is made on the basis of temporal correlation between malarial infection and subsequent neurological symptoms after its recovery, as there are no other definitive tests for this condition.[4] The criteria for 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.[4] As described earlier, its clinical feature can be in the form of encephalopathy of variable severity, ataxia, weakness of upper and lower extremities, and rarely seizures, motor aphasia, generalized myoclonus, and postural tremor.[3,5,6] Hereby, we are presenting a case of PMNS in an adolescent girl with isolated neuropsychiatric features, who responded favorably to corticosteroids. There are only a few adult case reports of PMNS presenting with isolated neuropsychiatric features available in the literature.[3]

CASE REPORT

A 12-year-old girl, second born to a nonconsanguineous couple, with premorbid normal development milestones and cognition, presented with acute onset neuropsychiatric manifestations for the past 3 days. She had irrelevant talking, was being aggressive to the caregiver, and even to unknown persons without provocation and restlessness. The child also developed an excessive preoccupation with unusual objects, such as combs, doorknobs, bottle caps, chocolate wrappers, which were not present before and altered sleep–wake cycles. She did not have any hallucinations, illusion, or delusion. However, the child had frequent mood fluctuations with alternating periods of inappropriately elated mood and periods of sadness without any definitive reason. At the same time, she was able to recognize caregivers and able to carry out simple one-step commands. She was also able to feed herself and was independent in other activities of daily living. There was no history of seizure, any focal deficit, gait instability, facial deviation, abnormal ocular movements, vision abnormality, or headache. There was no history of any accidental or habitual intoxication and recent animal bite.

On further questioning, the parents revealed that the child had an acute febrile illness (short duration fever with chills and rigor) about 1 month back. These febrile episodes were acute onset, high grade, spontaneous recovery after a few hours with profuse sweating and used to occur daily for 3 days before the caregivers sought medical advice. The child did not have any other associated symptoms, apart from severe body ache and myalgia, especially during the febrile episodes. Clinical examination at that time, as documented in previous prescriptions, had supposedly revealed pallor and splenomegaly with spleen palpable 2 cm below the left costal margin. The rest of the systemic examination was within normal limits at that time. Investigations during this febrile illness phase showed anemia (8 g/dL), and a positive rapid diagnostic test for malarial antigen. Peripheral smear and the quantitative buffy coat (QBC) test were also positive for malaria parasite (*Plasmodium falciparum*) with a parasitemia density of 14% (severe malaria). At that time, the white blood cell count was 7,800/μL, with 47% neutrophils and 49% lymphocytes. The total platelet count was 33,700/μL. Liver and renal function tests, as well as serum electrolytes, were within the normal range. Testing for common coinfections such as dengue, chikungunya, enteric fever, urinary tract infection, and other

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bacterial sepsis, including blood culture, were unremarkable. She was treated with oral artemether and lumefantrine fixed-dose combination for 3 days. She recovered fully without any complications within a week, and repeat QBC testing was negative for malaria parasites.

On examination at presentation to us, she was conscious and oriented to time, place, and person, but she had a slow response to questions with increased reaction time and deficit in executive function. She had a Mini-Mental Status Examination score of 18, which showed moderate impairment. There was no neurological deficit or signs of meningeal irritation. Other system examination was normal at presentation to our center.

Detailed neuropsychological evaluation according to Child Behavior Checklist revealed features of aggression, oppositional defiance, obsessive–compulsive behaviors, with the absence of insight. Conversion disorder, malingering, and recent emotional stressors were ruled out by performing House–Tree–Person Test.[7] There was also no definite history of any psychological stress in the family or school of the child. Urine for the toxicology screen was negative.

Repeat testing of peripheral smear for malaria parasite and QBC testing were negative. Serum electrolytes, antinuclear antibodies, antistreptolysin O, antineutrophil cytoplasmic antibodies, anti–double-stranded DNA antibodies, thyroid function test, and anti-thyroid peroxidase antibodies were all negative. Cerebrospinal fluid (CSF) examination was normal for cell counts (5 cells/uL, all lymphocytes), biochemistry (protein 42 mg/dL, sugar 67 mg/dL, and blood sugar 89 mg/dL), gram stain, microbiological culture, and autoimmune panel (for antibodies against NMDAR, AMPA1, AMPA2, GAD, CASPR, LGI-1, and $GABA_B$ receptor). The magnetic resonance imaging of the brain with contrast and electroencephalography were normal. Finally, a diagnosis of PMNS was concluded, in view of the temporal correlation with symptomatic malaria and after ruling out other possible causes.

She was started on intravenous methylprednisolone (1 g/day for 5 days) and oral olanzapine (5 mg/day). She started to show improvement in her clinical symptoms after about a week. Irrelevant talking and aggressive behavior gradually settled, and she started going to school after a month. At a follow-up after 6 months, there was no recurrence of neuropsychiatric symptoms. Hence, the antipsychotic, olanzapine was gradually tapered to 2.5 mg/day for two months and then stopped.

DISCUSSION

The aforementioned report describes an unusual presentation of PMNS, an already rare entity in pediatrics. The PMNS is still an enigmatic entity, and its exact pathogenesis remains yet to be elucidated. Up to date, 55 cases of PMNS have been reported in the literature. The youngest case among them was aged 6 years, as described by Mai et al.[1] Of these 55 cases, 42 were male, thereby having a male-to-female ratio of 3.2:1.

Apart from two cases with preceding *P. vivax* malaria, all previous cases had *P. falciparum* malaria.[8,9] Moreover, most of these cases occurred following severe and complicated falciparum malaria, unlike our case.[1] Initially, this fact was demonstrated by Nguyen et al.[1] in 1997 that PMNS is 300 times more common in patients with severe rather than uncomplicated malaria. The same investigators estimated the incidence of PMNS to around 1.2 per 1,000 malaria cases.[1] However, many of the previous investigators were of the opinion that this rare entity is grossly underreported, especially the mild cases.[4] Unfortunately, although malaria is still endemic in most of the developing countries and many health programs are going on at national and international levels, there are no exact surveillance data available regarding incidence or prevalence of PMNS.

In our literature review and pooled analysis, we found that the predominant clinical features were confusion (52%), seizure (33%), speech abnormalities (19%), and tremor (17%), although neuropsychiatric features, myoclonus, ataxia, headache, dizziness, weakness, somnolence, and nystagmus were found to be other rare presentations. Isolated neuropsychiatric features have been documented in about 7% of reported cases of PMNS, excluding patients with frank encephalopathy and confusion. The PMNS presenting with isolated neuropsychiatric features was described by Silva-Pinto and others.[10] The average parasitemia was found to be 18.5% in the 26 cases in which it was quantified. Although PMNS can occur up to 60 days following clearance of parasitemia, the median duration of onset of PMNS was found to be 13 days following resolution of initial illness in the reported patients.

Cerebrospinal fluid findings in PMNS may be completely normal, or it may show increased opening pressure, lymphocytic pleocytosis, and elevated protein, as documented in about 60% and 77% of the reported cases.[4] The PMNS with normal neuroimaging as in our case was reported by Zambito et al.[11] The MRI brain has been found to be unremarkable in most of the patients who had non–ADEM-like presentation and bilateral cerebral white matter lesions in patients with ADEM.[12] Rarely abnormal signal changes in the brain stem, thalamus, corona radiata, internal capsule, cerebellum, and even in the spinal cord have been reported.

Hsieh et al.[13] suggested obstruction of cerebral microvasculature by parasitized red blood cells, inducing cerebral hypoxemia. They also described markedly decreased radioactivity in brain single-photon emission computed tomography in a PMNS patient.[13] However, this mechanism is questionable as obstruction of microvasculature does not seem plausible because of the time interval of up to 60 days between malaria illness and PMNS. Currently, immune-mediated neuronal damage is considered the most plausible pathophysiological mechanism behind PMNS, although the putative malaria antigen has not yet been identified. The lag period between febrile illness of malaria and onset of neurological symptoms, as well as the favorable response to corticosteroids, favors the autoimmune hypothesis.[5,14,15] An increment of serum and CSF concentrations of inflammatory cytokines, such as TNF-α, IL 2 and IL 6, has been described in some cases of the delayed post-malaria cerebellar syndrome, which decreased following steroid therapy.[6] In certain recently reported cases, anti-neurexin and anti–voltage-gated potassium channel autoantibodies have been reported.[14]

Molecular mimicry by antibodies targeted toward antigens expressed by certain strains of *P. falciparum* that cross-react with antigens in the central nervous system (CNS) has also been postulated.[4] Although in the initial largest series to date, Nguyen et al. implicated mefloquine as a possible cause of PMNS as 17 of 22 patients (77%) in that series were previously treated with mefloquine.[1] But the recent case reports document only rare use of mefloquine, and this does not seem to account for most PMNS cases in the current situation.

The clinical recovery observed after treatment with corticosteroids in our case is consistent with a role for immunosuppression in the management of PMNS, but the value of this management strategy has not been proven. There is no standard treatment guideline for this rare syndrome, although the first case was reported in 1986, about 32 years back.[16] Most of the reported cases have documented uneventful recovery in mild cases managed conservatively. However, some reports have suggested beneficial effects of treatment with corticosteroids in cases of severe PMNS.[17] Steroid responsiveness was initially hypothetically proposed in PMNS cases because of its clinical resemblance to ADEM.[12] Schnorf et al.[18] have described two patients who continued to have worsening neurological symptoms until steroids were initiated, following which there was rapid recovery. Similarly, Hsieh et al.[13] described persistent ataxia in a patient with PMNS for 2 weeks until the use of corticosteroids, which resulted in dramatic recovery. Of 55 reported cases, 27 (49%) have received corticosteroids and all had rapid recovery within a few days of initiation of steroid therapy, except two patients who had a gradual recovery. Although most of these cases have ADEM-like presentation or cerebellar symptoms predominantly, few of those cases had confusion and predominant neuropsychiatric features. Of these 27 patients, 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 intravenous methylprednisolone for 3–5 days.[4,12] Interestingly, majority of the cases reported in the last decade considered the autoimmune pathogenesis strongly and used corticosteroids. Thus, treatment with corticosteroids may be considered as an option, albeit cautiously with confirmatory documentation of parasitemia clearance, as in our case, because corticosteroids, especially dexamethasone, have been found to be associated with unfavorable outcome in cerebral malaria.[19]

The case we presented has unique features of isolated neuropsychiatric symptoms at a young age with normal neuroimaging. The patient recovered with timely diagnosis and therapy with corticosteroids. Although most cases have a self-limiting course, physicians need to be aware of this rare entity. Clinicians should identify cases of PMNS early and consider cautious use of corticosteroids in severe cases.

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