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Conflicts of interest

The authors declare that they have no competing interest.

ABSTRACT:

Post-malaria neurological syndrome (PMNS) is a complication that occurs after recovery from a severe Plasmodium *falciparum* attack. Over the past two decades, the description of several imported cases has confirmed that this syndrome is a clearly distinct entity, different from other post malarial neurological disorders. However, the underlying mechanisms are not yet elucidated. Herein, we present five imported PMNS cases managed in Marseille, France. The detection of neuronal surface antibodies to an encephalitic syndrome of unknown origin allowed us to reveal positivity of anti Voltage-Gated-Potassium Chanel antibodies (anti VGKC) in one of them. Using treatment options from other autoimmune encephalitis has to be explored in patients with PMNS.

Key-words:

Malaria - Post-malaria neurological syndrome - *Plasmodium falciparum* - autoimmune encephalitis - anti VGKC antibody

Cerebral malaria is the most common neurological disorder that complicates severe *Plasmodium falciparum* infection. It has been linked with cerebral sequestration of parasitized red blood cells, cerebral inflammation and breakdown of blood-brain barrier[1]. In 1996, Nguyen et al. described a new entity they called post-malaria neurological syndrome (PMNS)[2]. It was reported as a neurological or psychiatric disorder occurring within two months of severe acute or cerebral malaria in a treated and cured patient (clearance of the parasites in the peripheral blood smears). This prospective study involved 22 patients in Vietnam suffering from clinical encephalopathy following confirmed infection with *P. falciparum*. The 22 patients recovered spontaneously without any specific treatment. Subsequently, 14 cases of PMNS following imported *P. falciparum* malaria were reported in the literature and reviewed by Markley et al in 2009[3]. This study has highlighted the characteristics common to both cases: PMNS has almost always been preceded by severe *Plasmodium falciparum* malaria; early clinical findings included altered consciousness, confusion, fever, generalized seizures, myoclonus, tremor, aphasia and/or psychosis. CSF study mostly exhibited lymphocytic pleocytosis with elevated protein; EEG revealed mild to severe encephalopathy and CT scan was still normal while MRI sometimes showed nonspecific signals. A rapid and effective response to corticosteroids in six of these cases led them to suggest an immune mechanism.

Case reports

Recently, we have reported the case of a PMNS in a 34-year-old white man with no significant medical history three weeks after having been cured from severe falciparum malaria following a trip in Benin and Mali without prophylaxis[4]. MRI was normal, EEG showed diffuse encephalopathy. CSF study, in addition to provide the PMNS expected elements (elevated protein and lymphocytic pleocytosis) showed intrathecal IgM synthesis with oligoclonal IgM bands. He was tested positive for antinuclear antibodies (titer 1/320), anti VGKC antibody (levels of 128 pmol/l; normal range < 72pmol/l) suggesting autoimmune encephalitis as no other diagnosis was documented. He dramatically responded to high dose intravenous (IV) corticosteroid. Latter, while isolated attention

disorder persisted, functional brain imaging with cerebral positron emission tomographic scan (PET-CT) disclosed abnormalities compatible with the diagnosis leading to repeat a 5-days high dose IV methylprednisolone. A new PET-CT several days after showed normal results while anti VGKC disappeared in plasma, as did serum antinuclear antibodies and oligoclonal CSF bands.

In recent years, four other non-infectious post-malarial encephalitis syndromes have been treated in our units in Marseille. Including the case mentioned above, they were five males aged 16 to 59 with no personal or familial history of neurological or psychiatric disease. All were returning from Sub-Saharan Africa and presented signs of encephalitis with seizure, ataxia, myoclonus and pyramidal syndrome a few weeks after having been treated and cured from a severe *P. falciparum* infection of which two had cerebral malaria. The latency observed ranged from 10 to 103 days. All the CSF showed elevated protein and four of them had lymphocytic pleocytosis. Performed in 4 patients, EEG revealed to be abnormal for all of them while MRI was abnormal for two patients only. MRI changes were for patient 1, bilateral frontal T2 FLAIR weighted hypersignal and for patient 3, right frontal T2 weighted hypersignal. A complete resolution of symptoms was observed in all 5 patients. Normalization of the clinical status was obtained between 7 and 28 days. Two of them were treated with corticosteroid and showed significant improvement. Details are presented in Table 1.

Discussion:

Our five cases met the previously established criteria for PMNS, with the exception of one case with a latency of 103 days but no other diagnosis. All developed this encephalitic syndrome after recent and cured severe falciparum malaria. We observed a male predominance, as previously reported[3]. Besides, our patients shared common clinical characteristics including confusion, seizure, fever, ataxia and tremor, as reported in the few previously published cases. In our study, pyramidal syndrome was often present. The median onset was 4 days in the Vietnamese study, 15 days for those reviewed in 2009 and is 17 days for us. CSF studies showed lymphocytic pleocytosis in four out of five patients and always raised protein which is superior to the data collected by Markley and

colleagues. The EEG is always abnormal when it is performed, perfectly congruent with the literature on the subject.

Interestingly, our last case[4] introduces various immune disorders that have never been tested or reported in PMNS before. This helped us clarifying the position of PMNS among other post infectious neurological syndromes. In front of this rapidly progressive encephalopathy of unclear etiology, founding low but significant positivity for antinuclear antibodies and lymphocytic CSF pleocytosis with intra-thecal synthesis of IgM led us to evoke an immune mediated process according to the current experience[5]. Antibody testing therefore performed showed positivity for antibodies against the voltage-gated potassium channel, associated to PET-CT abnormalities corroborating the hypothesis that PMNS precisely belongs to autoimmune encephalitis spectrum. Erasure of the anomalies three months after the acute phase is thus very consistent.

In order to assist physicians and practitioners and to facilitate identification of this infrequent clinical condition, Table 2 summarize the different neurological entities that could be encountered following a malaria treatment. In addition to PMNS, they are represented by delayed cerebellar ataxia (DCA) which is an acute inflammatory midline cerebellar ataxia[6], acute disseminated encephalomyelitis (ADEM) which is a central immune-mediated demyelinating disorder[7], acute inflammatory demyelinating polyradiculoneuropathy (AIDP) which is a monophasic peripheral demyelinating disease[8]. The nomenclature may be confusing since DCA and ADEM are autoimmune encephalitic syndromes but in this paper, the term autoimmune encephalitis refers specifically to the clinical finding as described in PMNS, associated with specific antibodies to the neuronal cell surface or synaptic proteins.

In ADEM, which broadly represent post infectious encephalopathies, many post infectious triggers have been described, mainly viral such as HSV[9], EBV[10], rubella[11], mumps[12] with some post vaccine forms (influenza, HBV, diphtheria-tetanus-polio)[13]. Bacterial infections of respiratory tract have been also implicated such as *Mycoplasma pneumoniae*[10], *Chlamydia pneumoniae*[14] and

Legionella pneumophila[15]. Parasitic etiologies of post infectious ADEM such as *Toxoplasma gondii* [16] are newly described in developing countries, however only about fourteen cases of ADEM following malaria cases are retrieved in the literature, *Plasmodium falciparum and vivax*[17] gathered. In comparison, PMNS appears to be a much more common cause of post-malarial encephalopathy.

Autoimmune encephalitis onset is also often preceded by infectious triggers. HSV-induced autoimmune encephalitis, mediated by antibodies against N-methyl-D-aspartate receptor (NMDAR) has already been described in patients presenting as HSV encephalitis relapse but with a negative polymerase chain reaction and a positivity of these antibodies[18].

Different primary mechanisms are proposed to explain how an infectious agent can induce autoimmunity. The oldest one is the molecular mimicry, supporting that there would be a cross-reaction of antibodies against the pathogen to autoantigens of the CNS. The hypothesis of a strong or prolonged inflammatory response during and after severe malaria or in the case of a relapse has already been evoked as a risk factor for developing such a syndrome. Thus, the persistence of the *P. falciparum*-specific HRP2 antigen, usually more than 28 days after eradication, could carry on the immune response leading to the pathology[19]. Finally the last explanation could be that exposure to previously protected neuronal antigens during infection could generate secondary development of synaptic autoimmunity. The latter hypothesis, which is preferred for HSV-induced NMDAR encephalitis, seems difficult to apply in our cases, since only two of them experienced cerebral malaria.

In autoimmune encephalitis, anti-VGKC antibodies target extracellular receptors of neuronal cell-surface or synaptic proteins and can be found in paraneoplastic syndromes or in auto-immune non paraneoplastic encephalitis[5]. The neuronal dysfunction is caused by a direct interaction between the antibody and the autoantigen and is potentially reversible. They are classically opposed to autoimmune encephalitis with antibodies against intracellular proteins in which T-cell mediated

cytotoxicity seems to be predominant, leading to an often irreversible neuronal dysfunction, with a lack of efficiency of the immunomodulating treatment[20].

Recently two cases of PMNS associated to neurexin-3alfa antibodies, another type of synaptic antibodies associated with autoimmune encephalitis, were reported. One is suspected and one is confirmed following malaria without severity criteria according to WHO but with a high parasitemia index (*P. falciparum* 8%), treated with high dose IV methylprednisolone[21,22]. Just like anti-VGKC detection in our patient, this suggests that patient with autoimmune propensity could develop autoimmune encephalitis presenting as a post infectious encephalitis, particularly following malaria.

All the cases we had in Marseille met the criteria for autoimmune encephalitis even though the antibodies were not systematically dosed. The wide and expanding spectrum of neuronal cell surface antibodies[23,24] raise the question of availability of the tests in healthcare settings. Retrospectively, knowing that this type of encephalitis is potentially responsive to specific immunotherapy should lead the clinician to provide himself the mean to appropriately screen patients with suspected autoimmune encephalitis. Therefore, we suggest that patients presenting with encephalitic syndrome after a severe and cured *P. falciparum* attack should first be tested for anti VGKC, anti LGI1 (leucine-rich glioma inactivated 1), anti CASPR2 (contactin-associated protein-like 2) and anti NMDAR which are the most frequently reported one. They should be tested both in serum and in CSF which provide a clean source of disease relevant antibodies. In negative case, other cell-surface/synaptic antigen (anti neurexin-3-alpha, anti GABAaR, anti GABAbR, anti DPPX, anti AMPAR)[24] should be tested. If these methodologies are not available in routine, aliquots should be sent to a center furnished with the adequate facilities for the future perspective of a better understanding of this disease. When discovered, those antibodies always requires for the clinician to rule out a neoplastic etiology.

However, it is important to specify that the antibody status is not mandatory to assume this diagnosis since they could be undetectable. Moreover, antibody testing could last several days, while

a prompt and appropriate immunomodulating treatment has to be discussed[25] if autoimmune encephalitis is the most probable diagnosis. According to many humoral-mediated autoimmune diseases, the first-line treatment of autoimmune encephalitis with surface neuronal antibodies may consists of high-dose IV corticosteroids followed by progressive reduction with oral corticosteroids[26]. Therapeutic options for first-line treatment or in refractory cases include intravenous immunoglobulin[27] or plasmapheresis[28]. In the same way, some authors[29] have reported the efficiency of corticosteroid use in severe and non-resolving cases of PMNS. Given the dysimmunity markers found in PMNS suggesting analogy to autoimmune encephalitis with extracellular target, proposing the same type of immunotherapy seems to be relevant in the absence of robust studies to guide the clinician. As for the clinician, his main challenge is to be absolutely certain that all infectious causes have been excluded before giving such therapy.

Conclusion:

Since malaria is still an endemic disease in Sub Saharan Africa, South East Asia, Latin America and because people keep on traveling without taking malaria prophylaxis, new PMNS cases are expected following severe *P. falciparum* malaria. Warning the clinician and more particularly neurologists and specialists in infectious disease seems to be relevant, indeed the chance to be confronted to this difficult diagnosis and to follow a case of encephalitis after malaria treatment is not null.

The autoimmune mechanisms responsible for post-malaria neurological syndrome are still poorly understood, however, the constant progress in the discovery of new antibodies and their involvement in similar syndromes such as autoimmune encephalitis could be of great value to understanding such an interesting disease.

The therapeutic concerns about how and when PMNS should be treated with corticosteroid or other immunotherapy is still questioned and bringing out antibodies associated with autoimmune encephalitis could be helpful in the discussion. As a parallel, specific treatment should not only be reserved for severe cases with profound conscious impairment or with an epileptic condition that

shows no sign of improvement. It should also be possible to give it to a patient complaining of even a mild cognitive neurological impairment, somatic, epileptic that is connected to the disease since those patients are usually young and active. However, all causes of infectious encephalitis must have been eliminated before treatment, especially a malaria relapse.

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5** [4]
Travel country	Congo (2006)	Ivory Coast (2007)	Ivory Coast (2007)	Benin, Togo, Burkina Faso (2008)	Mali, Benin (2015)
Sex	Male	Male	Male	Male	Male
Age (years)	59	16	53	30	34
Severe *P. falciparum*	Yes (cerebral malaria)	Yes (jaundice, hemoglobinuria, disseminated intravascular coagulation)	Yes (hypotension, jaundice, hemoglobinuria)	Yes (jaundice)	Yes (cerebral malaria)
Parasitemia	NA	NA	26%	NA	16%
Treatment	Quinine	Mefloquine	Quinine	Quinine	Artesunate-artemether/lumefantrine
Latency (days)	10	16	103	37	17
Symptoms	Confusion, dizziness, ataxia, fine tremor, aphasia, pyramidal syndrome	Ataxia, fine tremor, diplopia, fever	Confusion, ataxia, seizure, athetosis, fever	Confusion, impaired consciousness, ataxia, fine tremor, seizure, pyramidal syndrome, fever	Confusion, dizziness, ataxia, fine tremor, fever, seizure, pyramidal syndrome
CSF	3 WBC /mm3, protein 1.81 g/l	67 WBC /mm3, lymphocytic, protein 1.03g/l	38 WBC /mm3, lymphocytic, protein 1.7g/l	32 WBC /mm3, lymphocytic, protein 0.62g/l	180 WBC /mm3, lymphocytic, protein 2.03g/l Intrathecal synthesis
Antibodies	NA	NA	NA	NA	Antinuclear antibodies 1:320 AntiVGKC 128pmol/l
MRI	Bilateral frontal T2 FLAIR weighted hypersignal	Normal	Right frontal T2 weighted hypersignal	Normal	Normal
EEG	Abnormal	NS	Abnormal	Abnormal	Abnormal
Corticotherapy	No	No	No	Yes	Yes
Duration (days)	14	7	7	10	29

Table 1 Summary of the five PMNS cases diagnosed in Marseille

CSF : cerebrospinal fluid ; EEG : electroencephalogram ; MRI : magnetic resonance imagining ; NA : not available data ; VGKC : voltage gated potassium channel ; WBC : white blood cell count

	PMNS [3][4][21]	**DCA**[30][31]	**ADEM**[7][32][33]	**AIDP**[34]
Median latency before onset (days)	15 (range 2–57)	13 (range 3–41) with persisting parasitemia in one third of cases	10 (range 2–60)	12 (range 5–30)
Preceded by severe malaria	Yes (97%) and only with *P. falciparum*	No	Yes (92%) but 6 out of 14 cases involved *P. vivax*	No
Sex ratio (male/female)	2:1	8.25:1	0.44 :1	1.7:1
Mean age (years)	34 (range 6–61)	28 (range 16–56)	21 (range 1.5–54), half of the case are under 15	34 (range 10–63)
Clinical presentation	Encephalitis with impaired consciousness (77%), confusion (66%), central fever (50%), generalized seizure (33%), myoclonus (11%), aphasia (28%), tremor (23%), psychosis (17%)	Cerebellar ataxia without impaired consciousness or seizure (100%)	Typically multifocal neurological signs and encephalitis with focal or generalized seizures	Progressive ascending areflexic weakness (100%), sensory changes (79%), cranial nervepalsies (49%)
Cerebrospinal fluid	Lymphocytic pleocytosis (50%) and elevated protein (69%)	Always normal	Typically lymphocytic pleocytosis and elevated protein without oligoclonal band	Always elevated protein without pleocytosis
Antibodies	Anti VGKC Anti neurexin-3alfa	NR	No	NR Anti ganglioside?
Magnetic resonance imaging	Sometimes abnormal (33%), with increased T2 signal in cerebral grey and white matter, resolving in weeks	NA, normal in a case report	Constantly abnormal: cerebral, white matter lesions, cerebellar and basal ganglia involvement. Lesions typically persist several month	Needless
Electrophysiology	Always abnormal EEG: diffuse encephalopathy	Always normal EEG and ENMG	NR but typically abnormal EEG	Always abnormal ENMG : distal latency prolongation, conduction bloc, reduction of conduction velocity
Specific treatment	None (83%) Corticosteroids (17%)[3] IVIG? Plasmapheresis?	No	Corticosteroids (92%)	None (84%) IVIG (4%), plasmapheresis (4%)
Spontaneous relapses	NR	No	NR, but multiphasic forms exists in ADEM	No
Sequelae / Death	No / No	No / No	Yes (21%) / No	Rare (4%) / Frequent (77%) when respiratory failure is present (39%)

Table 2 Post infectious neurological complications likely to follow a recent cured malaria
ADEM : acute disseminated encephalomyelitis ; AIDP : acute inflammatory demyelinating polyradiculopathy ; DCA : delayed cerebellar ataxia ; EEG : electroencephalography ; ENMG ; electroneuromyography ; IGIV : intravenous immunoglobulins ; NA : not available NR : not reported; PMNS : post malaria neurological syndrome ; VGKC : voltage gated potassium channel

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