# Case report

## Post-malaria Myasthenia Gravis:

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### Abstract:

We report a nine-year-old girl who presented with complete drooping of the left eyelid and restriction of medial gaze following an attack of febrile illness. The child was admitted into a rural hospital where she was misdiagnosed and managed as a case of meningitis. She was referred to a tertiary children hospital when her condition was not improving and where she developed the eye signs. She was diagnosed as a case of severe malaria which responded well to quinine therapy. In our neurophysiology clinic, examination revealed partial unilateral left eye ptosis, weak frontalis, neck flexors, fingers extensors & knee flexors. Her investigations revealed positive neostigmine test, decremental response to repetitive nerve stimulation (-15.6%,nasalis), increased jitter in single-fibre electromyography (left frontalis & extensor-digitorum communis) and negative serology for myasthenia gravis antibodies. She showed remarkable improvement after pyridostigmine therapy which continued for three months. Regular follow-up showed no recurrence of her symptoms.

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### Introduction:

Myasthenia gravis (MG) is an autoimmune syndrome caused by failure of neuromuscular transmission, resulting from binding of autoantibodies to neuromuscular junction (NMJ) signaling proteins which include the nicotinic acetyl choline receptor or, less frequently, a muscle-specific tyrosine kinase, LRP4 and agrin.[1-3] The hypothesis of molecular mimicry has been proposed as a pathogenic mechanism to explain possible connection between infections and immune-mediated diseases.[4-8]

Extensive review of the literature revealed cases of MG following viral infections.[9-15] This case, to the best of our knowledge, is the first reported case of MG following malaria infection.

### Case History:

We report on a nine-years-girl admitted to a rural hospital with high grade fever, headache and mild neck stiffness. There was no photophobia or signs of increased intracranial pressure (ICP), no convulsions or loss of consciousness. She has been treated there empirically for the suspicion of meningitis. She was then referred to a specialized tertiary children hospital in the capital city Khartoum when her condition showed no improvement. She was properly investigated and the diagnosis of meningitis was excluded. She was diagnosed as a case of severe malaria infection which was confirmed by a positive blood film for plasmodium falciparum malaria with heavy parasitaemia and positive immune-chromatographic test (ICT). Complete blood count (CBC) was normal, showing normal total and differential WBC counts. During her stay in hospital, she developed complete drooping of the left eyelid with restriction of the gaze medially. No generalized fatigue, limb weakness or bulbar involvement. There was no history suggestive of recent viral infections or immunization. She responded very well to quinine therapy, but her eye signs improved partially. When she was referred to our neurophysiology clinic, re-examination revealed no papilledema, partial unilateral left eye ptosis (positive fatigable ptosis), weak frontalis, strong orbicularis oculi

& no ophthalmoplegia. Limb muscle bulk, strength and reflexes were normal except for mild weakness of neck flexors, fingers extensors & knee flexors (power grade 4). She showed dramatic complete response to intramuscular neostigmine. Repetitive nerve stimulation (RNS) studies at three Hz of the left facial nerve/nasalis showed decremental response of (-15.6%) as shown in figure 1. Single fibre electromyography (SFEMG) test was performed, using voluntary activation technique and concentric needle electrode. Mean jitter was increased in left frontalis (36 µs) [figure 2] & left extensor digitorum communis/EDC (38 µs) [figure 3] but normal in left Orbicularis Oculi (28 µs). Acetylcholine receptor (AChR) & muscle-specific tyrosine kinase (MuSK) antibodies were negative. She has been treated with pyridostigmine 30 mg qds. Seven days later, she showed remarkable improvement. She was almost back to normal [figure 4]. She was doing well on regular follow-up for 6 months. There was no recurrence of her symptoms following discontinuation of pyridostigmine therapy.

## Discussion:

MG can occur at any age. The male-to-female ratio in children with MG is 1:5.[16] It is estimated that between 10%-15% of the cases of myasthenia occur in the pediatric population.[17] Malaria is a common parasitic disease caused by a protozoan from the genus 'Plasmodium' of which there are four human species: Plasmodium vivax, Plasmodium falciparum, Plasmodium ovale and Plasmodium malariae. Several neurological complications are associated with complicated and severe falciparum malaria. Cerebral malaria is one of the most serious complications. Children are particularly more vulnerable to have this complication.[18] Falciparum malaria affects both young and old persons, but children are particularly at risk.[19] A wide spectrum of neurological complications have been described in some malaria cases including: spinal cord and peripheral nerve involvement (mono-neuritic syndromes, trigeminal neuralgia, retro-bulbar optic neuritis, involvement of ulnar, circumflex & lateral popliteal nerves) as well as transient muscle paralysis resembling periodic paralysis.[18,20] Some studies reported cases of Guillain-Barre-type polyneuropathy following vivax or falciparum malaria.[21-23]

Our case was a nine-year-old female with Plasmodium falciparum malaria who developed symptoms and signs of MG, few weeks following malaria infection. Clinical examination and electrophysiological studies confirmed the diagnosis of myasthenia, which was not previously reported in Plasmodium falciparum malaria cases. Viruses are commonly cited as triggers for autoimmune diseases. A previous study raised the possibility of viral infection as etiological factor for myasthenia gravis and described five myasthenic patients, whose symptoms began a few weeks after a proven viral infection.[9] In addition, two cases of post-infectious myasthenia gravis were reported by Felice and colleagues in 2005 [10]; a five year old boy who developed oculo-bulbar weakness two weeks following a varicella-zoster infection and a four- year- old boy who developed facial diplegia and dysarthria several weeks following a viral pharyngitis. A third case was reported in 2007 by Saha et al representing the youngest, and second reported, case of post-varicella myasthenia gravis.[12] Additional cases of anti-MuSK myasthenia gravis associated with Epstein-Barr virus [11] or HIV infections [13] had been reported. Another recent report described a case of anti-MuSK myasthenia gravis associated with acute hepatitis E infection (HEV) in a young, immune-competent patient in France, suggesting a potential role of HEV infection as a trigger of autoimmune disorders.[14] Another study reported six cases of seropositive myasthenia gravis (MG) developing several months after infection by West Nile Virus (WNV), all of them had elevated acetylcholine receptor (AChR) antibodies, and one had thymoma.[15]

The diagnostic sensitivity of the three laboratory tests [serum anti-acetylcholine receptor antibody (AChR-ab) assay, the RNS test, and the SFEMG] for MG, which was compared in 120 patients showed that SFEMG

was the most sensitive test, being abnormal in (92%) of cases, followed by the RNS test (77%) and the AChR-ab assay (73%).[24] The American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) has developed guidelines for electrodiagnostic testing for evaluation of MG.[1]

Anti-AChR antibodies are detectable only in 80%–90% of generalized MG patients and 30%–50% of ocular MG patients.[1,25,26] The Anti-MuSK autoantibody is positive in about 30-40% of patients with negative antibodies to the AchR. About 5% of MG patients have neither anti-AChR nor anti-MuSK antibodies[1] , similar to the findings in our patient.

The amplitude of the compound muscle action potential (CMAP) elicited by repetitive nerve stimulation is normal or only slightly reduced in patients without MG; while the amplitude of the fourth or fifth response to a train of low frequency nerve stimuli falls at least 10% from the initial value in myasthenic patients. This decrementing response to RNS is seen more often in proximal muscles, such as the facial muscles, biceps, deltoid, and trapezius than in hand muscles.[27] The repetitive nerve stimulation is the most commonly used method in electrophysiological diagnosis of MG. The test sensitivity is (80%–90%) in generalized MG patients and (30%–50%) in ocular MG patients. [1] SFEMG needs more patient cooperation and all of the methods (voluntary and axonal micro-stimulation) are technically demanding.[27] However, SFEMG has the highest sensitivity (95%–99%) and excludes the diagnosis of MG when it yields normal results.[1] It selectively records action potentials from a small number (usually two or three) of muscle fibers innervated by a single motor unit using either a standard single fiber electrode or a concentric needle EMG electrode with the smallest recording surface.[27] The amount of ACh released at the NMJ at different times has a small variability, resulting in comparable variations in the rise of end-plate potential (EPP) and the muscle fiber pair inter-potential intervals. This variability in successive inter-potential intervals is expressed using the mean consecutive difference (MCD), referred to as the 'jitter', is highly sensitive to neuromuscular transmission abnormalities. When there is a disorder of the NMJ, this will affect the time taken to depolarize the muscle fiber and there will be an increased variability resulting in an increase in jitter. And if the disorder is severe, there might be a complete failure of transmission down one nerve branch of the pair under study and the impulse will be blocked. In competent hands it is very accurate and should, perhaps, be considered as the gold standard in the diagnosis of the disorders of the NMJ.[28]

According to Myasthenia Gravis Foundation of America (MGFA) clinical classification[16], our patient belonged to Class II which is a mild disease that is characterized by ocular muscle weakness of any severity , in addition to mild weakness affecting other than the ocular muscles (e.g. forearm extensors). In our patient, the decremental response of (-15.6%) in the amplitude of the fourth response (CMAP) compared to the initial value in the Nasalis muscle was highly diagnostic (>10% cut off value) and specific as RNS has very high specificity in the diagnosis of MG.[29] In addition, the results of the highly sensitive SFEMG test of increased jitter in Frontalis and EDC muscles, confirmed that the NMJ in this case was abnormal.

The dramatic response to pyridostigmine in our patient probably reflects a mild reversible pathology which resolved with treatment of the primary trigger. The excellent response to acetylcholine esterase inhibitors treatment was also noticed in other post-viral MG cases[10, 12] suggesting that post-infectious MG is a relatively mild condition, and if diagnosed correctly, and treated promptly, the patient can lead a good quality life with self-recovery over a span of a few years.

## Conclusions and Recommendations:

In our case, interpreting the clinical manifestations with the electrophysiological and laboratory investigations, confirmed

malaria as the predisposing factor for the development of MG. However, this case report necessitates further detailed immunological studies that would document sequence homology between proteins involved in signaling at the neuromuscular junction (e.g. AChR) and plasmodium parasites so as to support a possible connection between malaria and myasthenia gravis.

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**Fig 1:** Repetitive nerve stimulation (RNS) of left Nasalis Muscle

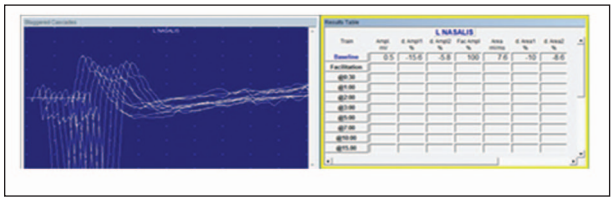

**Fig 2:** Voluntary-SFEMG of left Frontalis Muscle

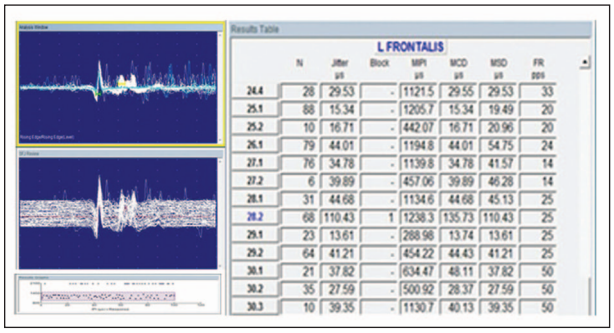

**Fig 3:** Voluntary-SFEMG of EDC Muscle

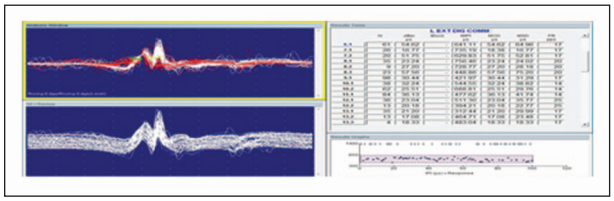

**Fig 4:** Photographic appearance of the patient's eye lids before and after treatment


## Legends of the Figures

**Fig 1:** Repetitive nerve stimulation of the left Nasalis muscle showing a decremental response of -15.6%

**Fig 2:** Voluntary-SFEMG of left Frontalis muscle showing increased jitter

**Fig 3:** Voluntary-SFEMG of EDC muscle showing increased jitter

**Fig 4:** Partial left upper eye lid drooping before treatment with pyridostigmine

(a). Complete recovery of the left upper eye lid drooping one week after starting treatment with pyridostigmine

(b). Complete recovery of the left upper eye lid drooping one week after starting treatment with pyridostigmine