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Artesunate-induced acute cerebellar dysfunction

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Abstract
A 78-year-old man presented with tremors and difficulty speaking fluently of 3 days duration. The tremor was of sudden onset and was first noticed on his right hand and subsequently involved all parts of his body. Two days prior to the onset of symptoms, he had taken artesunate tablets for acute malaria. Neurological examination revealed florid cerebellar signs (ataxia, nystagmus, dysmetria, dysdiadochokinesia). Brain magnetic resonance imaging (MRI) showed mild generalized cerebellar atrophy. Chest-X-ray and abdominopelvic ultrasound scan were essentially normal studies. Complete blood count, lipid profile, and renal indices were all within normal limits. Erythrocyte sedimentation rate was 33mm/hr, serum prostate specific antigen (PSA) was 4ng/ml. Blood film for malaria parasite was [+]. He was seronegative for HIV I and II. Syphilis serology (Venereal Disease Research Laboratory) was also negative. He was managed conservatively in the intensive care unit. His symptoms resolved dramatically over a five day period. He was subsequently discharged in good condition.

Keywords: artesunate, cerebellar dysfunction

1. Introduction
Artemisinin and its derivatives (artesunate, artemether, and dihydroartemisinin) are antimalarial drugs with a unique structure and mode of action. They are natural products derived from the plant *Artemisia annua* [1]. The first published report of their use in clinical trials for treatment of malaria was in 1979 [2]. Artemisinin and its derivatives are generally reported as being safe and well tolerated [3]. The World Health Organization (WHO) now recommends artemisinin-based combination therapy (ACT) for treating uncomplicated malaria. ACT is basically the combination an artemisinin derivative with another longer lasting drug that serves to reduce the risk of further resistance developing [4].
We describe the rare presentation of acute cerebellar dysfunction following ingestion of artesunate following an acute bout of malaria. To the best of our knowledge, this has not been previously reported in our country.

2. Case report
We present the case report of a 78-year-old man who is neither diabetic nor hypertensive who presented to us with tremors, difficulty with speaking fluently and inability to walk of 3 days duration. The tremor was of sudden onset and was first noticed on his right hand while trying to write. It subsequently became bilateral and progressed to involve his head, trunk, and lower limbs. He was said to be shaking uncontrollably necessitating his being unable to walk with the weakness of all his limbs. His speech was described as “speaking with pauses” with a jerky movement of both eyes. No history of dysphagia, seizures, loss of consciousness or vomiting, sensory complaints. There was no preceding history of head trauma, alcohol history was not significant. Two days prior to the onset of symptoms, he developed a fever which was presumed to be malaria. He took artesunate tablets and a few hours later he developed these symptoms.
Neurological examination revealed bilateral upbeat nystagmus with tremors of the tongue, head-trunk, and all limbs. There was generalized hypotonia with the power of 4/5 in all limbs. He had bilateral dysdiadochokinesis, dysmetria and impaired heel to shin coordination. Other systems examinations were intact. Our initial impression was that of an acute bi-hemispheric cerebellar disorder with possibilities being an acute ischaemic bi-hemispheric cerebellar stroke, drug-induced cerebellar disorder, and paraneoplastic cerebellar disorder.
Brain magnetic resonance imaging (MRI) showed mild generalized cerebellar atrophy. Chest-X-ray and abdominopelvic ultrasound scan were essentially normal studies. Complete blood count, lipid profile, and renal indices were all within normal limits. Erythrocyte sedimentation rate was 33mm/hour. His serum prostate specific antigen (PSA) was 4ng/ml. Blood film showed normocytic-normochromic red cells with adequate platelet distribution. He was seronegative for HIV I and II. Syphilis serology (Venereal Disease Research Laboratory) was also negative. He was managed conservatively in the intensive care unit. His symptoms resolved dramatically over a five day period. He was discharged in good condition.

3. Discussion
Although side-effects of artesunate are very rarely in our clinical practice, our patient's relatives could clearly recall the temporal relation between his ingestion of the drug and the evolution of his symptoms. The effect of artesunate in causing cerebellar dysfunction may have been facilitated by the age-related atrophy of the brain that occurs with aging. This would have predisposed his neuronal cells to susceptibility to the neurotoxic potential of artesunate. That he had full resolution of his symptoms is in keeping with observations that the neurotoxicity of artesunate in humans may be fully reversible. He did not have any feature of malignancy that would have been suggestive of a paraneoplastic cerebellar degeneration. However, paraneoplastic cerebellar run a slow and progressive course. Also, the symptoms of cerebellar dysfunction would

not have resolved dramatically on discontinuation of the drug. Orally administered artesunate has been found to be associated with clinical neurotoxicity in humans [5]. Intramuscular dosing is more toxic that oral route. This has been documented in some cases reports [6]. A syndrome of cerebellar dysfunction has been reported in a patient who took artesunate for four days [7]. The mechanism of neurotoxicity of artemisinin derivatives is similar in many respects to its mechanism of antimalarial action. They are sesquiterpene lactones. Cleavage of their endoperoxide bridge is catalyzed by complexes of iron or protein-bound iron and this generates free-radical intermediates that cause oxidative damage to the neuronal cell and parasite food vacuole [8, 9].

They also inhibit parasite calcium ATPase [10]. Features of cerebellar dysfunction such as ataxia and slurred speech have been reported with artesunate in animal studies [11]. Artemisinin-induced neurotoxicity in humans is said to be a rare and reversible adverse effect of a valuable and increasingly used group of antimalarial drugs [12].

4. Conclusion

Though a very rare side effect of artesunate seen in our practice, a very high index of suspicion is needed to make this diagnosis especially in elderly persons who are predisposed to age-related cerebellar degeneration.

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6. References

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