TMJ
Case report

Published by OJS
Doi: doi.org/10.4314/tmj.v30i1.295

OPEN ACCESS JOURNAL

Quinine associated cerebella ataxia responded with Rehabilitative therapy- A case report from a resource limited country Tanzania

*Piniel A. Kambey[1,2], Estomih P. Mtui[1,3], Haleluya I. Moshi[2], Elichilia R. Shao[4],

[1]Department of Anatomy and Neuroscience, Kilimanjaro Christian Medical University College, Moshi, Tanzania.
[2]Department of Physiotherapy, Kilimanjaro Christian Medical Center, Moshi, Tanzania.
[3]Division of Anatomy, Weill Cornel Medicine, New York, United States
[4]Department of Internal medicine, Kilimanjaro Christian Medical Center, Moshi, Tanzania.

***Corresponding author**

Dr. Piniel A. Kambey

E-mail: pinielalphayo@yahoo.com

TMJ
Case report

Published by OJS
Doi: doi.org/10.4314/tmj.v30i1.295

OPEN ACCESS JOURNAL

Abstract

Background
Quinine is among the commonly used drugs against malaria and it has been found to have effects against the central nervous system. The most contemporary documented effect is to the cerebellum. Its toxins can affect the layers of the cerebellum molecular (outermost layer), purkinje (middle) and granular layer (innermost). One of the observed effects is ataxia. Despite its effect, it is commonly used in our settings for treatment of complicated malaria.

Case presentation
A previously well-known 23-years old female, who is a local, second year medical student, presented to the town-based, district-level hospital with a two-day history of headache, joints pain, generalized body malaise, and vomiting. She did not travel to any endemic areas. During her clinical examination, she was noted to be febrile at 38'c. Examination on the central nervous system, cardio respiratory system was unremarkable. Blood slide for malaria parasite revealed 3mps/200wbc. The full blood picture findings were within the normal range except for the granulocytes which were slightly elevated. She was admitted and then injected with 600mg of Quinine (I.V) 8 hourly for 3 days and after she had finished the dose she started swaying with staggering gait. The condition worsened hence leading to a transfer to a resourceful centre for possible Magnetic resonance imaging (MRI). MRI could not depict any lesion in the brain neither the spinal cord. Neuro-rehabilitation was done and eventually after fourteen days the patient recovered.

Conclusion
Administration of quinine injection may have adverse effects on the postural and balance related structures of the brain. However, the resulting loss of balance and ataxia may resolve with time and with physical therapy. This case report ought to remind medical personnel attending patients especially those suffering from Malaria to be careful and observe the recommended dosage as it may compromise or cause effects to central nervous system. It also reminds urgent referral cases to opt for rehabilitation if undesired effects to the central nervous system occur.

Keywords: Quinine, cerebellum, ataxia, rehabilitation.

Published by OJS
Doi: doi.org/10.4314/tmj.v30i1.295

Background

A literature search has identified several causes of Central nervous system effects after malaria parasite clearance. Matias *et al.*, (2008) has found that the presence of impaired consciousness, ataxia, seizures, visual and auditory deficits is related with hypoglycemia (by malaria or quinine) or with the toxicity of anti-malarial drugs. Several diagnoses have been made for neurological manifestation after completely clearance of the parasite. Senanayake, Ariaratnam and Wijesundera, (1992) diagnosed it as delayed Cerebellar ataxia. Lawn *et al.*, (2003), van der Wal, Verhagen and Dofferhoff, (2005), Matias *et al.*, (2008) and Prendki *et al.*, (2008) named it Post malaria neurological syndrome. The pathogenic mechanisms involved in post malaria neurologic syndrome are not well understood, being admitted a possible immunological cause (Matias *et al.*, 2008).

Although the diagnosis being made is too general (does not specify the cause), there is a big association between quinine injection and cerebellar ataxia. Several case reports have shown that this neurologic manifestation occurs just few days after clearance of the parasite and finishing up with quinine dosage. A case report by van der Wal, Verhagen and Dofferhoff, (2005) has shown that a 53-year-old woman who was admitted because of malaria ended up with ataxia and other central nervous system manifestations just few days after finishing up a quinine dose 600 mg three times a day by intravenous infusion. Another case report by Senanayake, Ariaratnam and Wijesundera, (1992) has shown a case of 24-year-old Qatari male patient who admitted to Hamad General Hospital in December 1997 with a complaint of fever, headache, dizziness, and vomiting, a few days after returning from a visit to the Comoros Islands. After been treated with quinine sulphate 600 mg three times daily for three days and doxycycline 100 mg twice for a presumptive diagnosis of falciparum malaria, two days after stopping medication, he started to complain of dizziness and instability of gait. Similar cases have been documented from Congo Kinshasa (Duque *et al.*, 1984),

Published by OJS
Doi: doi.org/10.4314/tmj.v30i1.295

Gambia (Lawn *et al.*, 2003) and Ivory coast (Prendki *et al.*, 2008). Although we are not certain, we correlate the cause of ataxia with quinine injection.

Quinine is an antimalarial drug whose efficacy started being documented almost 400 years ago by Jesuit priests (Achan *et al.*, 2011). It is a cinchona alkaloid that belongs to the aryl amino alcohol group of drugs which is an extremely basic compound and is, therefore, always presented as a salt (Price, 2000). According to WHO, treatment of complicated malaria for adults, the first line should be intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, treatment will be completed with 3 days of artemisinin-based combination therapies. WHO has also strongly recommended that treatment of adults with uncomplicated P. falciparum malaria (except pregnant women in their first trimester), the first line should be one of the following artemisinin-based combination therapies (ACT): artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquin, dihydroartemisinin + piperaquine, artesunate + sulfadoxine–pyrimethamine (SP). Quinine plus doxycycline, tetracycline or clindamycin is recommended as second-line treatment for uncomplicated malaria (World Health Organization, 2015). Despite its effectiveness, it has been reported to have neurological effects (Pinto *et al.*, 2015). One among the reported neurological effects of quinine is cerebella ataxia (Med, 1999). To substantiate this, Ajibade and colleagues carried out a histological study to observe the micro structural changes on nissl substance in the cerebella cortex of adult wistar rats following quinine administration and found that there was degenerated nissl substance in the treated rats hence proved that quinine affects the synthesis of proteins in correlation with neuronal functions (Ajibade *et al.*, 2009). Gait alteration were also found following quinine administration to a wistar rat (Ashamu and Onaolapo, 2011).

Gait and balance disorders are often major causes of handicap in patients with cerebella ataxia. Although researches do not show which specific neuro rehabilitation should be given to a patient, there is evidence that they benefit from high-intensity

Published by OJS
Doi: doi.org/10.4314/tmj.v30i1.295

coordinative training (Marquer, Barbieri and Pe, 2014). In patients with cerebellar ataxia, coordinative training improves motor performance and reduces ataxia symptoms, enabling them to achieve personally meaningful goals in everyday life (Synofzik and Ilg, 2014).

Case Presentation

Demographic Information

We received a previously well-known 23-years old female, who is a local, second year medical student who presented to a district hospital in Moshi town. Her main complaints were headache, joints pain, generalized body malaise and vomiting. Her past medical history was non-contributory.

During her clinical assessment, she was febrile at 38^0C and on examining the central nervous system and cardio-respiratory system was unremarkable. Blood slide for malaria parasite revealed 3mps/200wbc. Results for full blood picture revealed only slightly elevated granulocyte count with the rest being within the normal values.

She was treated with 600mg of quinine injections (I.V) 8 hourly for 3 days due to unavailability of artesunate; which they would have administered as the first line drug. On the 5th day her condition changed as she started experiencing dizziness and later she developed cerebella ataxia. On the 7th day her condition worsened, she developed blurred vision and left lower limb weakness which necessitated her referral to an advanced health facility in Dar es Salaam. At this centre she was reviewed by a neurosurgeon who ordered a Magnetic Resonance imaging of the brain and spine whereas nothing abnormal could be detected. The neurosurgeon advised the family to take the patient to Kilimanjaro in one of the consultant and teaching hospitals for physiotherapy and follow up. When she arrived to this hospital, she was presenting with postural instability especially on standing and walking (**as per table 1**). As soon as she arrived back at Kilimanjaro, she commenced physiotherapy immediately.

Published by OJS
Doi: doi.org/10.4314/tmj.v30i1.295

Table 1: Results of Physical examination (as performed by a Physiotherapist). The posture control found abnormal, the rest parameters tested being normal.

	Clinical test	Findings
Postural control	Stance, narrow base	Sway, enhanced on narrow base
	Gait, tandem gait	Broad base of support stance and gait, more difficult on tandem walk
	Truncal control in sitting	Staggering and difficulties turning
		Good truncal control on sitting
Control of limb (movement arms and legs)	Alternating movements	Normal upper limbs alternations of movements
	Fast pointing movements	Accuracy of pointing (No over-shoot/ under-shoot)
	Sustained movements (finger-nose test)	No deviations from the movement trajectory, normal rhythm
Control of eye movement	Fixation	Clear fixation, neither gaze nor nystagmus
Control of speech	Conversation test syllables (coordination of diaphragm vocal cord)	No slurring, speech with clarity and fluency.
		Normal coordination of volume/breath

In order to be clear that this was not just sensory ataxia from the dorsal column of the spinal cord we performed Romberg's test (Agrawal *et al.*, 2011).

Romberg's test

We asked the patient to stand erect with feet together and eyes closed. She could not even stand by herself let alone with eyes closed. She could stand with support but with severe sway. So this suggested that the lesion was more likely to be on the cerebellum and not dorsal column of the spinal cord (Agrawal *et al.*, 2011).

Published by OJS
Doi: doi.org/10.4314/tmj.v30i1.295

OPEN ACCESS JOURNAL

Therapeutic intervention

Rehabilitative therapy

Physical therapy commenced immediately on arrival. It involved five phases. Phase one included psychotherapy whereby we counselled the patient and her parents about the health condition and what could have happened to the brain. This was necessary because the patient was anxious about her future and concerned about study sessions that she had missed out. In the same way, the parents were very concerned about their daughter and had started associating this health condition with witchery or evil spirits. To achieve relaxation, we also encouraged the patient to take deep breaths and relax, relaxed sitting and activities that may help distract her such as watching a movie or having friends around.

Phase two involved training from sitting to standing with a component of neck rotation on standing. From sitting position, the patient was asked to rise slowly without support. Initially she could do it but with severe sway, however she was asked to repeat the procedure several times and later she managed although with sway. A component of turning was added, where by the patient was asked to turn the head sideways, up and down while standing therefore taking three days as well.

After phase two was successful, we composed a more complex exercise on standing in phase three. The patient was asked to lift one leg up while eyes opened. She was able to perform this in a count of 5 then 10 as she built up confidence. She was instructed to repeat exercises for phases two and three until she achieved a safer stance. On the third day of training, she was able to perform exercises for phase two and three with eyes closed.

Phase four involved walking. Broad lines (15 feet long, 1 feet width) were drawn on the floor using chalk. She was instructed to walk along the lines. In the beginning, she managed although with severe sway which eventually disappeared slowly with repeated training. To make it a bit complex, after we were satisfied, we reduced the width of the two lines so that she walked on a narrow space.

Published by OJS
Doi: doi.org/10.4314/tmj.v30i1.295

We tested her mobility by using timed up and go test. We instructed her to wear her regular footwear and sit back in a standard arm chair and a line of 10 feet away on the floor was identified.

Instructions to the patient**:** When I say **"Go,"** I want you to:

1. Stand up from the chair
2. Walk to the line on the floor at your normal pace
3. Turn
4. Walk back to the chair at your normal pace
5. Sit down again

On the word **"Go"** we began timing. We stopped timing after patient has sat back down and recorded time in seconds. The times used to complete the circle were recorded as follows.

This shows that there was a good progress from day one of phase IV to day three. She was instructed to do the same program at home and two weeks later the patient had a better and safer gait and could walk alone without any assistance and therefore we needed her to continue with activities of daily living and more complex exercise like stairs climbing at home.

Table 2: Time used by the patient to complete the circle. The gait of the patient increased progressively.

	Day 1 of phase iv (Time-seconds/milliseconds)	**Day 2 of phase iv(Time-seconds/milliseconds)**	**Day 3 of phase iv(Time-seconds/milliseconds)**
1st circle	45.54	42.41	30.08
2nd circle	45.30	42.41	30.05

Published by OJS
Doi: doi.org/10.4314/tmj.v30i1.295

3rd circle	45.32	42.37	30.07
4th circle	45.31	42.34	30.04
5th circle	45. 30	42.24	30.01
MEAN	45.35	42.35	30.05

Discussion

The cerebellum is largely involved in co-ordination and persons, whose cerebellum is affected, will generally present with clumsy and unsteady movements (Eluwa *et al.*, 2017). The neurotoxin effect of quinine is the matter of concern. Ashamu and Onaolapo, (2011) had observed the postural instability after administration of quinine injection to a patient suffering from malaria. This concurs with the case we reported, since the patient developed postural instability 72 hours after being treated with quinine (van der Wal, Verhagen and Dofferhoff, 2005). These selective behavioral changes with gait disturbance could indicate brain damage especially on the cerebellum. Quinine intoxication results in hypokalaemia, hypoglycaemia, cardiotoxicity, visual symptoms (also blindness) and neurological features as convulsions, coma and ataxia (Mishra and Newton, 2010). Although other features did not manifest, ataxia noted in our case. There is strong evidence that neurological symptoms develop during or shortly after the usage of quinine (van der Wal, Verhagen and Dofferhoff, 2005). The literatures has found that the post malaria neurological syndrome develops 14 days and above (Senanayake, 1987). In contrast to our case, the symptoms developed 3 days after the last gift of quinine, and therefore quinine intoxication was likely rather than post malaria neurological syndrome.

In contrast with this study, it has been noted that patients with cerebella ataxia, present with slurred speech (Lawn *et al.*, 2003). This was not observed in our case and the reason might be the less severity of the micro structural effects to the cerebellum.

In this study it was noted that it is good to be clear on the type of ataxia so as to avoid generalizing its presentation. We performed Romberg's test and found that it was

Published by OJS
Doi: doi.org/10.4314/tmj.v30i1.295

positive. This corresponds with the basics instructions on why, when and how to perform Romberg's test (Agrawal *et al.*, 2011).

In our study, the micro structural lesion could not be depicted by using magnetic resonance imaging. However, a study done in Nigeria by Ashamu and Onaolapo, (2011) on micro structural observations on nissl substances in the cerebellar cortex of adult wistar rats following quinine administration, (quinine intramuscular 6mg/kg body weight as a start dose, followed by 8mg/kg body weight on an 8 hourly basis for seven days) revealed that there was less intense stain and degenerated nissl substance in the treated rats and these degenerative changes may affect synthesis of proteins in correlation with neuronal functions. This could signify that micro structural damage of brain tissues cannot be depicted by magnetic resonance imaging but rather histological studies can elucidate the effect. Absence of histological findings from the case that we are presenting obscures the possibility of ascertaining exact tissues which were temporarily affected in this regard. It may be such as what was reported by Ashamu and colleagues, that it was the purkinje cells of the cerebellum that were affected, in a study done using an animal model (Ashamu and Onaolapo, 2011). However, with the clinical findings that we were able to gather, we argue that the cerebellum was temporarily affected in this case.

Several studies have reported self-limiting neurological manifestation. A woman travelled from Kenya to Nijmegen, later diagnosed to have post malaria neurological syndrome after been recovered from malaria, treated with high dose of prednisone and after 30 days recovered fully (van der Wal, Verhagen and Dofferhoff, 2005). Similarly to a case reported in Qatar, it was self-limiting, with spontaneous and complete recovery within three months (Senanayake, Ariaratnam and Wijesundera, 1992). Our study has a unique component which involved Physiotherapy, thus accelerated the recovery process. It only took 14 days for the recovery to take place. Although we query that its quinine which has caused effects to the cerebellum but still physiotherapy can reduce the recovery time.

Published by OJS
Doi: doi.org/10.4314/tmj.v30i1.295

Conclusion

For the first time in Tanzania, we report and document a rare case of quinine associated cerebella ataxia responded after physiotherapy. There was no evidence of the brain structural changes with MRI however physical examination could be used to confirm the effect to the brain.

Declaration

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Abbreviations

MRI: Magnetic Resonance Imaging

WHO: World Health Organization.

Authors' contributions

PK was the responsible practitioner, did the physiotherapy part, carried out the literature research and drafted the manuscript. EM, HM, ES supervised the clinical process and reviewed the manuscript critically. PK produced the first draft which was reviewed by all authors.

All authors read and approved the final manuscript.

Acknowledgements

We thank the patient involved for giving us consent to publication of the data.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

Data supporting this case are available.

Published by OJS
Doi: doi.org/10.4314/tmj.v30i1.295

Ethics approval and consent to participate

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal

Funding

Not applicable.

References

1. Achan, (2011) **'Quinine , an old anti - malarial drug in a modern world : role in the treatment of malaria'**, *Malaria Journal*, 10(144), pp. 1–12. doi: 10.1186/1475.
2. Agrawal, (2011) **'The Modified Romberg Balance Test: Normative Data in U.S. Adults'**, pp. 1309–1311.
3. Ajibade, (2009) **'Microstructural observations on Nissl substances in the cerebellar cortex of adult Wistar rats following quinine administration'**, *Tropical Journal of Pharmaceutical Research*, 8(2), pp. 105–109.
4. Ashamu, E. A. and Onaolapo, A. Y. (2011) **'Suppression of exploration and locomotion in adult Wistar rats following quinine administration'**, 3(March), pp. 32–37.
5. Duque, (1984) **'Case report Plasmodium falciparum malaria , bilateral sixth cranial nerve palsy and delayed cerebellar ataxia'.**
6. Eluwa, (2017) **'EJPMR histological changes in the cerebellum of adult wistar rats following administration of ethanolic extracts of lemongrass and mango bark'**, 4(7), pp. 269–273.
7. Lawn, (2003) **'Postmalaria Neurological Syndrome: Two Cases from The Gambia', *Clinical Infectious Diseases***, 36(2), pp. e29–e31. doi: 10.1086/344774.
8. Marquer, A., Barbieri, G. and Pe, D. (2014) **'The assessment and treatment of postural disorders in cerebellar ataxia : A systematic review'**, 57, pp. 67–78. doi: 10.1016/j.rehab.2014.01.002.

9. Matias, (2008) **'Post-malaria neurologic syndrome'**, *Acta medica portuguesa*, 21(4), pp. 387–390.
10. Med, Q. J. (1999) **'QJM Cerebellar syndrome in Plasmodium'**, (i), pp. 233–234.
11. Mishra, S. K. and Newton, C. R. J. C. (2010) **'UKPMC Funders Group Diagnosis and management of the neurological complications of falciparum malaria'**, 5(4), pp. 189–198. doi: 10.1038/nrneurol.2009.23.
12. Pinto, W. B. V. de R. (2015) **'Ataxias cerebelares não-progressivas e lesão cerebelar aguda prévia indeterminada: Uma condição clínica misteriosa',** *Arquivos de Neuro-Psiquiatria*, 73(10), pp. 823–827. doi: 10.1590/0004-282X20150119.
13. Prendki, (2008) **'Short report: Post-malaria neurological syndrome - Two cases in patients of African origin'**, *American Journal of Tropical Medicine and Hygiene*, 78(5), pp. 699–701.
14. Price, R. N. (2000) **'Artemisinin drugs: novel antimalarial agents.', *Expert opinion on investigational drugs***, 9(8), pp. 1815–1827. doi: 10.1517/13543784.9.8.1815.
15. Senanayake, N. (1987) **'Delayed cerebellar ataxia: A new complication of falciparum malaria?'**, *British Medical Journal (Clinical research ed.)*, 294(6582), pp. 1253–1254. doi: 10.1136/bmj.294.6582.1253.
16. Senanayake, N., Ariaratnam, A. and Wijesundera, M. de S. (1992) **'Delayed cerebellar ataxia (DCA) complicating falciparum malaria'**, *Proceedings of the International Medical Congress 29th July 2nd August*, 105(May 1998), pp. 1998–1999.
17. Synofzik, M. and Ilg, W. (2014) **'Motor Training in Degenerative Spinocerebellar Disease : Ataxia-Specific Improvements by Intensive Physiotherapy and Exergames'**. Hindawi Publishing Corporation, 2014. doi: 10.1155/2014/583507.
18. van der Wal, G., Verhagen, W. I. M. and Dofferhoff, A. S. M. (2005) **'Neurological complications following Plasmodium falciparum infection.**', *The Netherlands*

Published by OJS
Doi: doi.org/10.4314/tmj.v30i1.295

journal of medicine, 63(5), pp. 180–3. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15952488.

19. World Health Organization (2015) '**Treatment of Severe Malaria', *Guidelines For The Treatment of Malaria*,** pp. 71–88. doi: 10.1016/0035-9203(91)90261-V.