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CASE REPORT

Quinine in the Treatment of Malignant Migrating Partial Seizures in Infancy: A Case Report

[1]ABEER YOUSAF ALI MATTER, [2*]AALIA AKHTAR HAYAT
[1]Department of Neuropsychiatry, Maternity and Children Hospital, Makkah al Mukarma, Saudi Arabia; email: mattera88@gmail.com
[2]Department of Neuropsychiatry, Maternity and Children Hospital, Makkah al Mukarma, email: aaliah_hayat@hotmail.com
**Corresponding author: Aalia Akhtar Hayat, email: aaliah_hayat@hotmail.com*

ABSTRACT

The syndrome of malignant migrating partial seizures in infancy was first described by Coppola and colleagues in 1995. The International League Against Epilepsy defines this form of epilepsy as a seizure onset in the first 6 months of life, occurrence of almost continuous migrating polymorphous focal seizures, combined with multifocal ictal EEG discharges, and progressive deterioration of psychomotor development. Most cases are pharmacoresistant and have poor outcomes. A lot of publications described the trial of several medications such as Stiripentol, Rufinamide, Cannabidiol, and finally Ketogenic diet, to control the refractory devastating seizures. We describe a 13-month-old girl with malignant migrating partial seizures in infancy who was started on Quinine for the control of her refractory seizures after the trial of multiple antiepileptic medications that failed to control her seizures, including Clonazepam, Carbamazepine, Phenobarbitone, Phyntion, Midazolam, Valproate, Perampanel & Ketogenic diet, all were tried by different combination at different times. Finally, as malignant migrating partial seizures in infancy are sometimes linked to K channelopathy, a trial of Quinine was given in a dose of 30mg/kg/d. Patients showed an excellent response with control of clinical & electrographic seizures. Now she is seizure-free for five months and undergoing physiotherapy. She started rolling over but doesn't have much improvement in motor milestones, is not following or cooing, and is unable to say clear words.

Keywords: MMPSI – malignant migrating partial seizures in infancy- Quinine – Intractable epilepsy- CPLANE-1 gene defect

INTRODUCTION

The syndrome of malignant migrating partial seizures in infancy (MMPSI) was first described by Coppola and colleagues in 1995.

The International League Against Epilepsy defines this form of epilepsy as follows: seizure onset in the first 6 months of life, occurrence of almost continuous migrating polymorphous focal seizures, combined with multifocal ictal EEG discharges, and progressive deterioration of psychomotor development.

Most cases of (MMPSI) are pharmacoresistant, and have poor outcome. Lot of publications described the trial of several medications as Stiripentol, Rufinamide(1), Levetiracetam(2), Bromide(3), Ketogenic diet(4), & finally Cannabidiol(5), to control the refractory devastating seizures.

The most common cause of (MMPSI) is a gain of function mutation in the potassium channel KCNT1.Quinidine as an antiarrhythmic drug is a partial antagonist of KCNT1 and was shown to be effective in a trial of this condition in one case reported 2014 (6).

We report a case of a child with migrating partial seizures of infancy who was given quinidine after the trial of multiple antiepileptic medications that failed to control her seizures. She was shifted to quinine after failure of quinidine therapy and quinine resulted in clinical & electrographic seizure freedom.

PATIENT INFORMATION: We describe a now 20-month-old girl, product of full term pregnancy, normal vaginal delivery; she was well until the age of 3 months when she started to develop attacks of apnea & abnormal breathing pattern that was misdiagnosed as Gastro esophageal reflux disease (GERD) initially at a private facility. EEG was done at that time & was normal. Later her apnea was associated with some focal seizures in the form of unrolling of the eyes for which she was started on Clonazepam & Carbamazepine.

CLINICAL FINDINGS: She presented at our hospital at the age of seven months with a chest infection that was associated with an increase of seizure frequency.

Her seizures at that time were in the form of repetitive right facial twitching & rapid eye blinking associated with cyanosis and disturbed level of consciousness. She had about 4 attacks /day. A Loading dose of Phenytoin 15mg/kg and Levetiracetam 30mg/kg was started and later kept on a maintenance dose of 5mg Phenytoin and 30mg/kg Levetiracetam.

She had no dysmorphic features- weight, height & head circumference were all below the 5% percentile. She had severe hypotonia with head lag and poor sucking with swallowing problems, so nasogastric tube was inserted.

DIAGNOSTIC ASSESSMENT: Her metabolic screen was negative. General brain atrophy was evident by volume loss with prominent sulci and gyri, thinning of corpus callosum and dilated extra axial spaces in T1 and T2 images of brain MRI. Fig 1a and b

Fig 1a: T1 sequence of brain MRI showing mild brain atrophy

THERAPEUTIC INTERVENTION: She developed status epilepticus partials for which she was admitted to Pediatric intensive care unit under video EEG monitor. Phenobarbitone, Phenytoin and Midazolam failed to control her seizures, so Thiopental was introduced & dose increased upto7 mg/kg/hr, her seizures were controlled but she showed clinical & electrographic relapse with the trial of Thiopental withdrawal. Finally after 10days we gradually stopped Thiopental. She had ongoing brief focal seizures that were not affecting her hemodynamically. She was kept on Levetiracetam 60mg/kg/d, phenobarbitone 8mg/kg/d and Ketogenic diet was started. The Fat: (Protein-

carbohydrate) ratio was increased from 1:1 up to 3.5:1. Her seizures were brief lasting 2-3 min, but frequent up to 30 times per day. Sometimes they did last more than 5 min for which she received Diazepam & Phenytoin loading as required. Perampanel was tried for some time with no benefit, so it was stopped. A trial of Clobazam, Valproate and a course of IVIG were given with no improvement of her clinical & electrographic seizures. Fig 2a and 2b show the right and left occipital discharges on EEG.

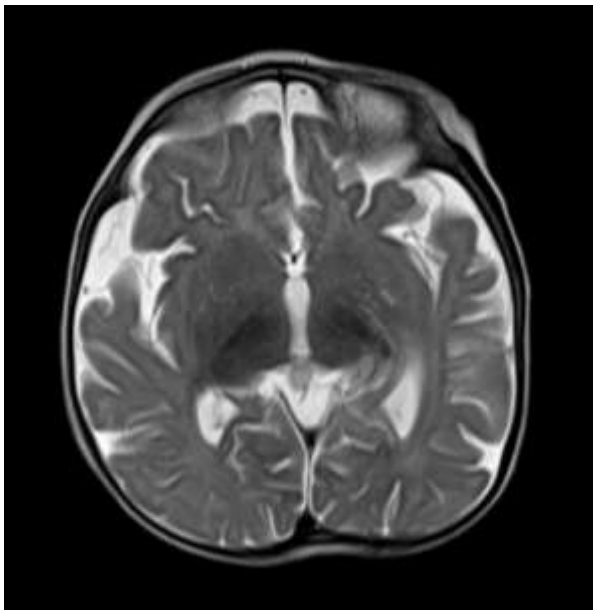


Fig 1b: T2 sequence of brain MRI showing thinning of corpus callosum

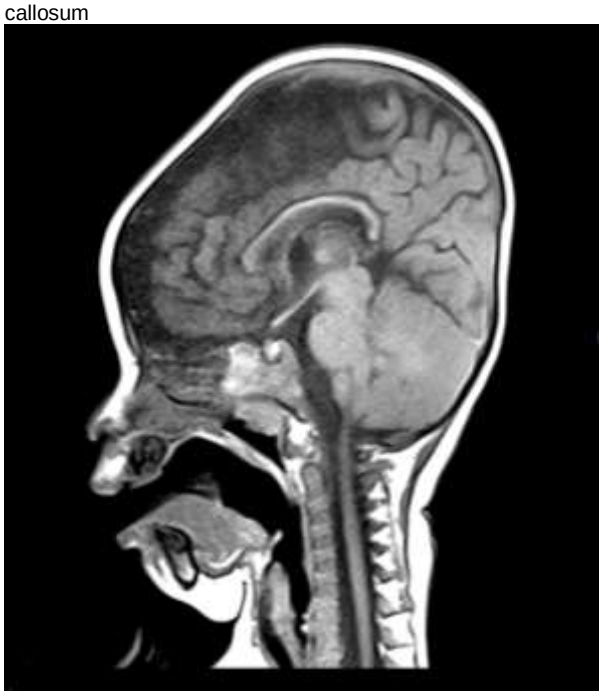


Fig 2a: Left Occipital discharges.

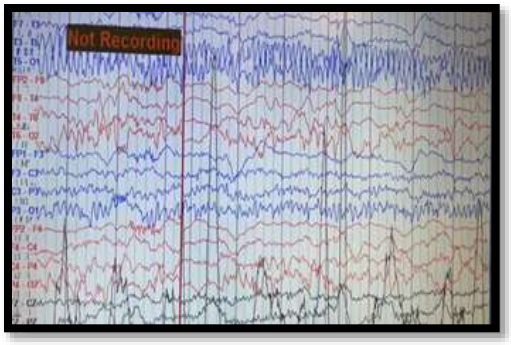
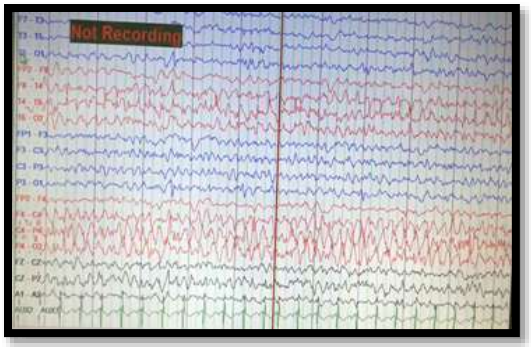


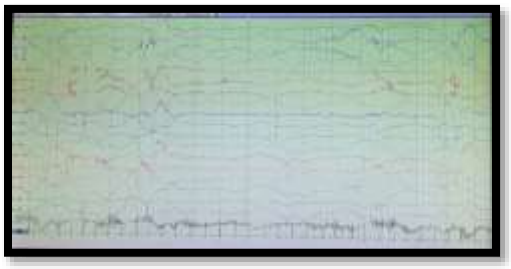
Fig 2b: Right occipital discharges.



Whole exome sequencing was done and showed Ciliogenesis and Planar Polarity Effector 1 (CPLANE1) gene defect (variance of unknown significance).

Finally as malignant migrating partial seizures in infancy was sometimes linked to K channelopathy, a trial of Quinine was given in a dose of 30mg/kg/d, the seizures stopped after the 2nd dose. When we tried to substitute quinine with quinidine, as previous trials were recommending quinidine, she had a relapse & seizures ensued again, so we kept her on Quinine 30mg/kg/d. Patients showed excellent response with control of clinical & electrographic seizures, Her EEG after Quinine therapy is shown in Fig 3.

Fig 3: EEG after quinine therapy.



FOLLOW UP AND OUTCOMES: So she was discharged on quinine 30mg/kg/d, phenobarbitone 7mg/kg/d, Topamax 10mg/kg/d and a Ketogenic diet. On follow up, repeated EEGs, ECG as well as the labs, i.e. liver function tests, renal function tests, bone profile and electrolytes were normal. Ketogenic diet was discontinued and other medications were continued at the same doses.

Currently, on her last follow up in the clinic she was seizure free. She is undergoing physiotherapy, has partial

head control and has started to roll over. She has started cooing, but has no clear words or babbles.

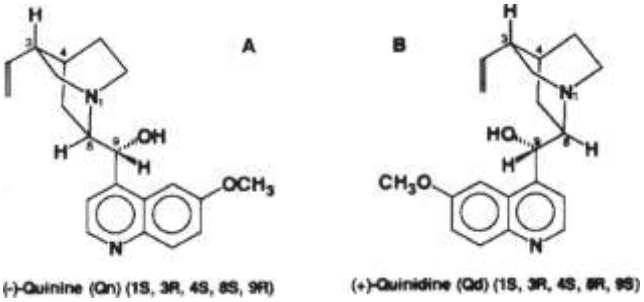
DISCUSSION

The most common cause of (MMPSI) is a gain of functional mutation in the potassium channel KCNT1.The antiarrhythmic drug Quinidine is a partial antagonist of KCNT1 and hence may be a candidate drug for treatment of this condition. Treatment with Quinidine was correlated with a marked reduction in seizure frequency and improved psychomotor development in a case reported in 2014(6).

Quinine has been in use for more than three centuries to treat severe plasmodium falciparum malaria before the introduction of the artemsinins in malaria endemic areas. It has antipyretic, analgesic and anti-inflammatory properties and has been used to treat arthritis and systemic lupus erythematosus (SLE).

The only structural difference between Quinine, Quinidine is their three-dimensional configuration, the geometry of the 9-hydroxyl group and the quinuclidine ring system. This conformation of the hydroxyl and amine groups was thought to be important for the difference of their antimalarial potency, and might be responsible for Quinidine's antiepileptic action as well. Fig 4 shows chemical structure of Quinine and Quinidine.

Fig 4: Conformation of hydroxyl and amine groups in quinine and quinidine.



There were no studies or case reports on the use of Quinine in epilepsy patients without malaria cited in literature, however, some Randomized Control trials comparing Quinine to other artemether in treatment of cerebral malaria presenting with seizures had been reported in literature.

The first RCT comparing the use of Quinine to artemether in patients with cerebral malaria, involved children (n=576). Mean age in the Quinine and Artemether group was 46 months and 48 months respectively. Significantly less children in the Quinine group developed seizures than those in the Artemether group (38.5% Vs. 28.1%, p=0.01) (7).

The second RCT was a large pragmatic trial comparing Quinine to artesunate involving children (n=5425) from sub-Saharan Africa. Median age (Interquartile range) was 2.8 years (1.6–4.2) in the artesunate group and 2.9 years (1.7–4.3) in the Quinine group. Prevalence of seizures after 6 hours of admission was 10.1% in the Quinine group and 8.3% in the artesunate group (p=0.0199) (8).

The third RCT (n=109) had three arms involving Quinine, Artemisinin and Artesunate. Median age was 5, 7 and 6 years respectively. 11% of the children in the Artemisinin group, 8% in the Artesunate group and 3% in the Quinine group developed convulsions. (19)

All trials concluded that there was no clinical evidence to suggest an antiepileptic property of Quinine. At best it was shown to have lesser potential for causing seizure as a probable side effect when compared to Artemether (10).

CONCLUSIONS AND IMPLICATIONS: Not any published literature supporting the use of Quinine as an antiepileptic drug in non-malaria cases could be found to support this. Reporting of this case might however open a new avenue and possibility of improvement in cases resistant to other recommended treatments of epilepsy. A trial of Quinine might yield favorable outcome in treatment resistant or non-responding cases. Further studies with better design and larger sample size need to be conducted in order to explore the possibility of Quinine being effective in the treatment of epilepsy in general and Malignant Migrating Partial Seizures in Infancy in particular.

REFERENCES

1. Vendrame, M., Poduri, A., Loddenkemper, T., Kluger, G., Coppola, G., & Kothare, S. V. (2011). Treatment of malignant migrating partial epilepsy of infancy with rufinamide: Report of five cases. Epileptic Disorders.2011;13(1), 18–21. https://doi.org/10.1684/epd.2011.0406
2. Hmaimess, G., Kadhim, H., Nassogne, M.-C., Bonnier, C., & van Rijckevorsel, K. Levetiracetam in a neonate with malignant migrating partial seizures. Pediatric Neurology.2006; 34(1), 55–59. https://doi.org/10.1016/j.pediatrneurol.2005.06.011
3. Okuda, K., Yasuhara, A., Kamei, A., Araki, A., Kitamura, N., & Kobayashi, Y. Successful control with bromide of two patients with malignant migrating partial seizures in infancy. Brain & Development.2000; 22(1), 56–59. https://doi.org/10.1016/s0387-7604(99)00108-4
4. François, L. L., Manel, V., Rousselle, C., & David, M. [Ketogenic regime as anti-epileptic treatment: Its use in 29 epileptic children]. Archives De Pediatrie: Organe Officiel De La Societe Francaise De Pediatrie.2003; 10(4), 300–306. https://doi.org/10.1016/s0929-693x(03)00030-7
5. Saade, D., & Joshi, C. Pure cannabidiol in the treatment of malignant migrating partial seizures in infancy: A case report. Pediatric Neurology.2015; 52(5), 544–547. https://doi.org/10.1016/j.pediatrneurol.2015.02.008
6. Bearden, D., Strong, A., Ehnot, J., DiGiovine, M., Dlugos, D., & Goldberg, E. M. Targeted treatment of migrating partial seizures of infancy with quinidine. Annals of Neurology.2014; 76(3), 457–461. https://doi.org/10.1002/ana.24229
7. Van Hensbroek, M. B., Onyiorah, E., Jaffar, S., Schneider, G., Palmer, A., Frenkel, J., Enwere, G., Forck, S., Nusmeijer, A., Bennett, S., Greenwood, B., & Kwiatkowski, D. A Trial of Artemether or Quinine in Children with Cerebral Malaria. New England Journal of Medicine.1996; 335(2), 69–75. https://doi.org/10.1056/NEJM199607113350201
8. Dondorp, A. M., Fanello, C. I., Hendriksen, I. C. E., Gomes, E., Seni, A., Chhaganlal, K. D., Bojang, K., Olaosebikan, R., Anunobi, N., Maitland, K., Kivaya, E., Agbenyega, T., Nguah, S. B., Evans, J., Gesase, S., Kahabuka, C., Mtove, G., Nadjm, B., Deen, J., … AQUAMAT group. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): An open-label, randomised trial. Lancet. 2010;376(9753), 1647–1657. https://doi.org/10.1016/S0140-6736(10)61924-1
9. Cao, X. T., Bethell, D. B., Pham, T. P., Ta, T. T., Tran, T. N., Nguyen, T. T., Pham, T. T., Nguyen, T. T., Day, N. P., & White, N. J. Comparison of artemisinin suppositories, intramuscular artesunate and intravenous quinine for the treatment of severe childhood malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene.1997; 91(3),33 5–342. https://doi.org/10.1016/s0035-9203(97)90099-7
10. Clifford, M., Leah, M., & Charles, N. Antiepileptic properties of Quinine: A systematic review. Annals of Neurosciences.2012; 19(1), 14–20. https://doi.org/10.5214/ans.0972.7531.180404