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BURDEN OF CEREBRAL MALARIA; PERSONALIZED MEDICINE TO THE RESCUE: A REVIEW OF THE NEW CONCEPT

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ABSTRACT

Malaria is endemic in over 100 countries and about 240 million people are at risk of developing the disease. Annually, about 20-30 million clinical malaria cases occur globally with over 1 million deaths. In 2017 alone, the global malaria parasitic infection amounted to about 200 million and death toll from the disease was almost half a million people. Unfortunately, almost 90% of all deaths due to malaria occur in tropical sub-Saharan Africa. Hence, with current rate of drug resistance and its continuing to spread, a better understanding of the molecular basis and mechanisms that control the malaria parasite's life cycle is paramount to developing improved therapies and possible prophylaxes. The recent single-cell technology that investigate the genes in individual malaria parasites, which reveals the genetic processes each parasite undergoes as it moves through its complicated life cycle may lead to uncovering of previously hidden ways in which genes are used for the development of malaria parasites in the blood. Single-cell sequencing allows for studying the activity of each gene in individual parasites and for understanding how malaria parasites move through the life cycle and how much individual-to-individual variation there is among parasite stages that are most vulnerable to drugs and vaccines. This may eventually lead to establishment of single-cell data from the host tissues the parasite must colonize to complete its life cycle, including the mosquito gut cells and the mammalian host liver cells. Currently there is growing interest in novel precision therapies based on molecular findings. For instance, Quinidine reverses the in vitro gain of function seen with *KCNT1* mutations in epilepsy with migrating focal seizures of infancy, and a clinical response to quinidine has been observed. Additionally, in a patient with a mutation in *GRIN2A*, encoding a glutamate receptor subunit, memantine therapy appeared effective. Furthermore, the recent discovery of the importance of mutations in *DEPDC5*, which is now

known to be a regulator of mTOR, raises the possibility of treatment with rapamycin analogues. All of these observations clearly support the possible role of precision medicine in evaluation and management of Cerebral malaria. Certainly, in the coming years with single-cell technology which is a form of personalized medicine, management of cerebral malaria will experience a transformation in the direction of personalized diagnosis and treatment, taking the individual aspects of the patient and his or her disease into consideration.

KEYWORDS: Burden of Cerebral Malaria, Epileptic seizures, Personalized medicine, New concept.

INTRODUCTION

Malaria is one of the oldest human afflictions caused by an infectious agent. It is a communicable disease caused by Plasmodium species typified by Plasmodium falciparum (P. falciparum).[1,2] Plasmodium falciparum is the only specie that appears to directly affect the central nervous system causing neurological sequelae.[1,3,4] In the tropical African countries like Nigeria, Malaria was often part of the turbulence of nations that is ravage by diseases war and poverty. It has been reported that up to 75% cases of plasmodium falciparum infections occur in sub-Saharan Africa.[5] Among all cases of severe malaria caused by plasmodium falciparum, Cerebral Malaria (CM) stands as the most severe neurological presentation of acute plasmodium falciparum infection. Cerebral malaria is histopathologically characterized by swelling of small blood vessels such as cerebral capillaries and venules with both parasitized and non- parasitized red blood cells.[6] There may be impairment in the structural and physiological dysfunction of the blood-brain barrier.[7] There is histological evidence of cerebral edema, with petechial haemorrhages.[8] Durck's granuloma may also be seen due to accumulation of glial cells surrounding hemorrhagic foci.[9-13]

Clinical Features of Cerebral Malaria: In adults the onset of cerebral malaria is usually gradual, with high fever and increasing drowsiness. Convulsions are present in about 15% of cases, while about 50% of paediatric cases may have seizures.[14,15] Seizures are most frequently tonic-clonic generalized convulsions, but may also be focal. Neurological examination usually revealed a febrile patient with no obvious signs of meningial irritation. However, hyperextension of the neck and mild rigidity may occur in severely ill patients.[15]

Role of personalized medicine: Currently there is growing interest in novel precision therapies based on molecular findings. For instance, Quinidine reverses the in vitro gain of function seen with *KCNT1* mutations in epilepsy with migrating focal seizures of infancy, and a clinical response to quinidine has been observed.[16-20] Additionally, in a patient with a mutation in *GRIN2A*, encoding a glutamate receptor subunit, memantine therapy appeared effective.[21] The recent discovery of the importance of mutations in *DEPDC5*.[19-23] which is now known to be a regulator of mTOR, raises the possibility of treatment with rapamycin analogues. All of these observations clearly support the possible role of precision medicine in evaluation and management of epilepsy. Furthermore, it is important to note that, epileptic encephalopathies associated with mutations in *SCN2A* and *SCN8A* are gradually becoming better defined.[24,25] With precision medicine the profile of drug responsiveness may be different as the proteins encoded are localized to excitatory neurons, whereas the *SCN1A* protein appears to be mainly on inhibitory interneurons. Indeed, for *SCN8A* encephalopathy, sodium channel blockers may be effective in some cases.[25]

Another epileptic variant that would benefit from precision medicine is Pyridoxine-dependent epilepsy and a related disorder, pyridoxamine 5'-phosphate oxidase deficiency, owing to mutations in *PNPO*, these are well-known, though rare, infantile epilepsy disorders, generally diagnosed by clinical suspicion and response to pyridoxine and pyridoxal 5'-phosphate respectively, mutation detection in *ALDH7A1* can provide confirmation and be used to rapidly screen at-risk siblings although the relationship of mutations to treatment response remains unclear.[26]

Prospectus: The prospect of precision medicine in detecting, managing and preventing epilepsy is essentially based on its impact in the overall healthcare provision especially in resource limited settings such as tropical Sub-Saharan African region. In developed societies, progress has been seen in areas such as ongoing genomic projects, bench to clinic translational medicine, increasing advance toward genetic evaluation, and conventional medicine to precision medicine. In the rapid transformation in molecular biology, healthcare provision is inclining to patient's satisfaction on disease management, with the view of having drug therapies that would be more effective with reduced incident of adverse effects to ensure improved quality of life. Regulatory agencies are also being pressured to approve drug therapies with minimum adverse reactions and increase efficacy. Therefore, although conventional medicine cannot be completely ruled out, it is evident that personalized

medicine is shaping the future of medicine and stands a promising chance of overtaking conventional means of managing chronic neurological diseases such as epilepsy.

CONCLUSION

Cerebral malaria is a life threatening complication of malaria; it affects children more than adult. Significant number of survivors suffer from long-term neurological sequelae such as epilepsy. Thus, high index of suspicion is needed for early diagnosis and effective treatment. Furthermore, with advent of precision medicine, a specific molecular diagnosis, where possible, adds greatly to the accuracy of treatment and avoidance of unnecessary adverse effect of drugs used in the management of epilepsy. Therefore, the promise of personalized medicine in epilepsy care is becoming a reality and may eventually form a centre stage in care for patients with epilepsy.

REFERENCES

1. Carter R, Mendis KN Evolutionary and historical aspects of the burden of malaria. Clin Microbiol Rev., 2002; 15: 564-594.
2. Singh B, Kim Sung L, Matusop A, Radhakrishnan A, Shamsul SS, et al. A large focus of naturally acquired Plasmodium knowlesi infections in human beings. Lancet, 2004; 363: 1017-1024.
3. Mung'Ala-Odera V, Snow RW, Newton CR The burden of the neurocognitive impairment associated with Plasmodium falciparum malaria in sub-saharan Africa. Am J Trop Med Hyg., 2004; 71: 64-70.
4. Newton CR, Hien TT, White N Cerebral malaria. J Neurol Neurosurg Psychiatry, 2000; 69: 433-441.
5. WHO Global Malaria Situation. World Malaria Report 2005. WHO/HTM/MAL/2005.1102 ed. Volume WHO/HTM/MAL/2005.1102. Geneva: RBM/UNICEF/ World Health Organization, 2005; 5-17.
6. MacPherson GG, Warrell MJ, White NJ, Looareesuwan S, Warrell DA Human cerebral malaria. A quantitative ultrastructural analysis of parasitized erythrocyte sequestration. Am J Pathol, 1985; 119: 385-401.
7. Brown H, Hien TT, Day N, Mai NT, Chuong LV, et al. Evidence of blood-brain barrier dysfunction in human cerebral malaria. Neuropathol Appl Neurobiol, 1999; 25: 331-340.

8. Walker O, Salako LA, Sowunmi A, Thomas JO, Sodeine O, et al. Prognostic risk factors and post mortem findings in cerebral malaria in children. Trans R Soc Trop Med Hyg., 1992; 86: 491-493.
9. Warrell DA Cerebral malaria: clinical features, pathophysiology and treatment. Ann Trop Med Parasitol, 1997; 91: 875-884.
10. Dharmeshkumar NP, Pradeep P, Surti MM, Agarwal SB Clinical Manifestations of Complicated Malaria- An Overview. J India Acad Clin Med, 2003; 4: 323-331.
11. Looareesuwan S, Warrell DA, White NJ, Sutharasamai P, Chanthavanich P, et al. Do patients with cerebral malaria have cerebral oedema? A computed tomography study. Lancet, 1983; 1: 434-437.
12. Looareesuwan S, Wilairatana P, Krishna S, Kendall B, Vannaphan S, et al. Magnetic resonance imaging of the brain in patients with cerebral malaria. Clin Infect Dis., 1995; 21: 300-309.
13. Newton CR, Peshu N, Kendall B, Kirkham FJ, Sowunmi A, et al. Brain swelling and ischaemia in Kenyans with cerebral malaria. Arch Dis Child, 1994; 70: 281-287.
14. Oluwayemi OI, Brown BJ, Oyedeji OA, Adegoke SA, Adebami OJ, et al. Clinical and laboratory predictors of outcome in cerebral malaria in suburban Nigeria. J Infect Dev Ctries, 2013; 7: 600-607.
15. World Health Organization Severe falciparum malaria, Communicable Diseases Cluster. Trans R Soc Trop Med Hyg, 2000; 94(1): S1-90.
16. Milligan CJ, Li M, Gazina EV, Heron SE, Nair U, Trager C, Reid CA, Venkat A, Younkin DP, Dlugos DJ, Petrovski S, Goldstein DB, Dibbens LM, Scheffer IE, Berkovic SF, Petrou S. KCNT1 gain of function in 2 epilepsy phenotypes is reversed by quinidine. *Ann Neurol* 2014; 75: 581–590.
17. Bearden D, Strong A, Ehnot J, DiGiovine M, Dlugos D, Goldberg EM. Targeted treatment of migrating partial seizures of infancy with quinidine. *Ann Neurol*, 2014; 76: 457–461.
18. Pierson TM, Yuan H, Marsh ED, Fuentes-Fajardo K, Adams DR, Markello T, Golas G, Simeonov DR, Holloman C, Tankovic A, Karamchandani MM, Schreiber JM, Mullikin JC; PhD for the NISC Comparative Sequencing Program, Tifft CJ, Toro C, Boerkoel CF, Traynelis SF, Gahl WA. *GRIN2A* mutation and early-onset epileptic encephalopathy: Personalized therapy with memantine. *Ann Clin Transl Neurol*, 2014; 1: 190–198.
19. Dibbens LM, de Vries B, Donatello S, Heron SE, Hodgson BL, Chintawar S, Crompton DE, Hughes JN, Bellows ST, Klein KM, Callenbach PM, Corbett MA, Gardner AE,

Kivity S, Iona X, Regan BM, Weller CM, Crimmins D, O'Brien TJ, Guerrero-López R, Mulley JC, Dubeau F, Licchetta L, Bisulli F, Cossette P, Thomas PQ, Gecz J, Serratosa J, Brouwer OF, Andermann F, Andermann E, van den Maagdenberg AM, Pandolfo M, Berkovic SF, Scheffer IE. Mutations in DEPDC5 cause familial focal epilepsy with variable foci. *Nat Genet*, 2013; 45: 546–551.

20. Picard F, Makrythanasis P, Navarro V, Ishida S, de Bellescize J, Ville D, Weckhuysen S, Fosselle E, Suls A, De Jonghe P, Vasselon Raina M, Lesca G, Depienne C, An-Gourfinkel I, Vlaicu M, Baulac M, Mundwiller E, Couarch P, Combi R, Ferini-Strambi L, Gambardella A, Antonarakis SE, Leguern E, Steinlein O, Baulac S. DEPDC5 mutations in families presenting as autosomal dominant nocturnal frontal lobe epilepsy. *Neurology*, 2014; 82: 2101–2106.
21. Scheffer IE, Heron SE, Regan BM, Mandelstam S, Crompton DE, Hodgson BL, Licchetta L, Provini F, Bisulli F, Vadlamudi L, Gecz J, Connelly A, Tinuper P, Ricos MG, Berkovic SF, Dibbens LM. Mutations in mTOR regulator DEPDC5 cause focal epilepsy with brain malformations. *Ann Neurol*, 2014; 75: 782–787.
22. Baulac S, Ishida S, Marsan E, Miquel C, Biraben A, Nguyen DK, Nordli D, Cossette P, Nguyen S, Lambrecq V, Vlaicu M, Daniau M, Bielle F, Andermann E, Andermann F, Leguern E, Chassoux F, Picard F. Familial focal epilepsy with focal cortical dysplasia due to DEPDC5 mutations. *Ann Neurol*, 2015; 77: 675–683.
23. D'Gama AM, Geng Y, Couto JA, Martin B, Boyle EA, LaCoursiere CM, Hossain A, Hatem NE, Barry BJ, Kwiatkowski DJ, Vinters HV, Barkovich AJ, Shendure J, Mathern GW, Walsh CA, Poduri A. Mammalian target of rapamycin pathway mutations cause hemimegalencephaly and focal cortical dysplasia. *Ann Neurol*, 2015; 77: 720–725.
24. Nakamura K, Kato M, Osaka H, Yamashita S, Nakagawa E, Haginoya K, Tohyama J, Okuda M, Wada T, Shimakawa S, Imai K, Takeshita S, Ishiwata H, Lev D, Lerman-Sagie T, Cervantes-Barragán DE, Villarroel CE, Ohfu M, Writzl K, Gnidovec Strazisar B, Hirabayashi S, Chitayat D, Myles Reid D, Nishiyama K, Kodera H, Nakashima M, Tsurusaki Y, Miyake N, Hayasaka K, Matsumoto N, Saitsu H. Clinical spectrum of SCN2A mutations expanding to Ohtahara syndrome. *Neurology*, 2013; 81: 992–998.
25. Larsen J, Carvill GL, Gardella E, Kluger G, Schmiedel G, Barisic N, Depienne C, Brilstra E, Mang Y, Nielsen JE, Kirkpatrick M, Goudie D, Goldman R, Jähn JA, Jepsen B, Gill D, Döcker M, Biskup S, McMahon JM, Koeleman B, Harris M, Braun K, de Kovel CG, Marini C, Specchio N, Djémié T, Weckhuysen S, Tommerup N, Troncoso M, Troncoso L, Bevot A, Wolff M, Hjalgrim H, Guerrini R, Scheffer IE, Mefford HC, Møller RS; Euro

EPINOMICS RES Consortium CRP. The phenotypic spectrum of SCN8A encephalopathy. *Neurology*, 2015; 84: 480–489.

26. Mills PB, Camuzeaux SS, Footitt EJ, Mills KA, Gissen P, Fisher L, Das KB, Varadkar SM, Zuberi S, McWilliam R, Stödberg T, Plecko B, Baumgartner MR, Maier O, Calvert S, Riney K, Wolf NI,. Epilepsy due to PNPO mutations: Genotype, environment and treatment affect presentation and outcome. *Brain*, 2014; 137: 1350–1360.