Neonates at risk of early neonatal malaria in Kigali University Teaching Hospital (UTHK) from 2013 to 2016

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ABSTRACT:

Cases: A review of case-files of 17 neonates whose mothers had a malaria diagnosis at the time of labor to better understand how neonates were investigated, diagnosed and/or treated for early neonatal malaria during the admission period. Four neonates were found to have neonatal malaria.

Results: All four neonates who were diagnosed and treated for malaria presented with non-specific clinical features of neonatal sepsis. Two had malaria in differential diagnoses at admission. All cases had a malaria positive blood film. Two of the four neonates with neonatal malaria died. The investigation and management of these exposed neonates was not found to be consistent or standardized.

Conclusion: Neonatal malaria infection presents with similar features to neonatal sepsis and can be deadly if diagnosis and treatment is delayed. Consensus work is needed to develop a standardized approach to the investigation and management of neonates exposed to malaria during pregnancy.

Key words (MeSH): Congenital malaria; Malaria; Falciparum; neonatal sepsis; Infectious Disease Transmission, Vertical

INTRODUCTION

In the first half of the twentieth century, the incidence of congenital malaria in endemic areas was understood to be very low with rates between 0.18% and 0.95% of the total neonate population [1]. Studies carried out in Sub-Saharan Africa between 2008 and 2010 have shown a variable prevalence of congenital malaria from 0% to 46%, though more recent multicenter studies have reported lower rates of 4-6% [2]. A case-series of congenital malaria from Rwanda has previously been described from a second tertiary centre [3].

Malaria infection or relapse during pregnancy poses a risk to the life of the mother and fetus. Researchers have found a significant association with poor fetal and neonatal outcomes such as spontaneous abortion, perinatal mortality, low birth weight and prematurity [4]. For physicians caring for newborns this is an important topic. Due to the nature of and rates of neonatal malaria trial data is limited and therefore we remain dependent on information from case-studies and case-series. The aim of this case-series is to describe the clinical presentation and outcomes of neonates exposed to maternal malaria and/or with an early diagnosis of malaria, recorded in an inner-city tertiary neonatology unit between 2013 and 2016 in Rwanda. Neonates of mothers with malaria diagnosis are including to give a description of how these neonates are investigated and managed

CASE PRESENTATIONS

Cases were found from the neonatology unit of University Teaching Hospital of Kigali (UTHK). UTHK is the largest, public, tertiary referral hospital in Rwanda, located in Kigali city, and also serves as a teaching hospital for the University of Rwanda. The cases were identified using the Neonatal Database (NDB) from the neonatology unit at UTHK. The database has collected prospective data from 2013 and as of December 2016 contained data on more than 2600 neonates. The database was searched from the 1st July 2013 to 1st December 2016 to identify two groups of neonates (Table 1):

1. All neonates who had blood smear confirmed malaria
2. All neonates whose mothers had blood smear confirmed malaria during labor

The Case-files of the 17 neonates identified were then retrospectively reviewed. This case-series did not search for mothers on the obstetric unit who were malaria positive, rather we focused on newborns admitted to the neonatal unit. It is therefore possible that there were further cases of exposed neonates that are not described here.

Transmission

In all 17 cases the neonates had mothers who had been diagnosed with malaria either during pregnancy or labour and 4 neonates (23.5%) were found to be malaria positive. The retrospective nature of this case-review means that we are unable to define if the mothers had clinical malaria or had asymptomatic parasitaemia. This because the information was not always provided in details on the neonatal admission charts.

Only two of the neonates met the criteria for "congenital malaria", with malaria confirmed in the first 7 days of life. Two neonates were diagnosed on days 14 and 30 of life. It is possible that these newborns could have been infected after delivery, though in light of the maternal history this would be less likely.

Clinical features and perinatal history of neonates with malaria

Three malaria positive neonates were born prematurely at 28, 30 and 33weeks. Two were born by spontaneous vaginal delivery and two delivered by emergency caesarean. There are no details on the indications for their delivery and so we cannot confidently confer their premature births to the maternal malaria infection. Two babies, both of whom were premature, were hypothermic on admission which is likely to reflect the risk of hypothermia which is established in prematurity [5].

Among other abnormalities were abnormal respiratory and heart rates and abnormal oxygen saturation; these abnormalities also are not uncommon in the settings of prematurity and maternal fever. Therefore, the clinical features that these neonates presented are common in neonatal infection and warranted their investigation and treatment for neonatal sepsis. Because congenital malaria is less common than neonatal sepsis in the settings of maternal fever, prematurity and abnormal neonatal physical exam, it is a diagnosis of exclusion and therefore easy to miss.

Investigations/Diagnosis of neonates with malaria

Two of the four neonates had malaria in the differential diagnosis at the time of admission and the remaining two neonates were investigated for malaria after lack of response to treatment for neonatal sepsis. The diagnosis of malaria was made from blood smear. No parasitemia level was available in any of the cases. There was no umbilical blood sampled or placental samples taken. Parasitemia level and placenta sampling are not routinely done for malaria diagnosis in our settings.

Management and outcomes of neonates with malaria

The diagnoses of malaria were made on days 2, 3, 14 and 30 of admission and were treated with anti-malarials for 4, 3, 2 and 10 days respectively. The neonate who was diagnosed with malaria on the fourteenth day of admission had been ill since birth and did not improve with treatment for neonatal sepsis, it is therefore reasonable to suspect that the initial illness was due to malaria.

Two malaria positive neonates were treated successfully with 3 and 10 days of treatment and discharged home. Two neonates with a diagnosis of malaria died. Both these neonates died two days after the diagnosis was made. Both neonates received standard neonatal care appropriate in the settings of prematurity and potential neonatal sepsis.

Neonates with risk of malaria (maternal malaria)

Among 17 identified cases, 13 (76%) tested negative for malaria throughout their admission. However, they did have risk factors for malaria: all were exposed to risk from mothers with a diagnosis of malaria and had non-specific clinical signs which could be attributed to malaria. We did not review the maternal notes and are therefore unaware of the indication of malaria testing in the mothers.

The diagnostic approach for these 13 neonates who were not found to have malaria took into account neonatal sepsis and other conditions such as hypoglycemia. Investigation for malaria was erratic. Thirteen neonates (76.4 %) were investigated for congenital malaria only with a blood film, Rapid Diagnostic Testing(RDT) methods are not used in referral hospitals. Of the 9 neonates who had negative blood films, none had a repeat blood film.

Their initial reasons of admission were either prematurity, neonatal infection risk or both. Two neonates were discharged within 24 hours of their admission to the neonatal unit. Because our database is limited to the period of admission we are unaware if any neonates developed malaria after discharge.

Eleven of all 13 neonates who tested negative for malaria were admitted and treated empirically for neonatal sepsis while the investigations were ongoing. The outcome of malaria-negative neonates was relatively better than that of the other 4 neonates who tested positive for malaria: 1/13 (7.7%) died compared with 2/4 (50%). The long hospital stay of the neonates was mainly related to their prematurity rather than their malaria management; severe maternal malaria threatens pregnancy and therefore predisposes to prematurity.

DISCUSSION

Transmission

Congenital malaria results from the transplacental transmission of asexual forms of Plasmodium parasites [6]. The mechanism of transmission of the parasites from mother to fetus is not yet fully understood. Malaria parasites reach the foetal blood by crossing the disrupted placental barrier either during pregnancy or during labour with uterine contractions "pushing" parasites into the foetal circulation, the exo-erythrocytic forms passing through the chorionic villi or through alteration of the placental barriers by several factors including premature abruption lesions, caused by the parasites themselves or their toxic metabolites, and repeated hyperthermic [1], [7], [8]

Studies have shown that congenital malaria in endemic areas is rare due to high levels of maternal antibodies, the presence of fetal hemoglobin which retards Plasmodium maturation and the para-amino benzoic acid (PABA) deficient breast milk which deprives the parasites of folic acid essential for their [1], [7] Combined these confer to neonates a relatively decreased risk of clinical disease during the first month of life because malaria clears spontaneously [2], [9], [10] however in light of the cases we have identified, there is enough evidence to support clinicians being aware of neonatal malaria as a potential cause of symptoms.

Symptoms and signs of congenital malaria

Clinical manifestations of congenital malaria are not apparent at birth and it lacks many of the classical presentation of malaria infection, thus the diagnosis

requires a very high index of [6], [11] has been noted that congenital malaria can be an incidental finding on blood [9], [11]

In symptomatic neonates, fever is almost always present. Infection may also be associated with non-specific symptoms such as poor feeding, irritability, lethargy or symptoms of gastrointestinal irritation such as diarrhea and vomiting [4], [6], [8], [9], [12]–[19].

Investigations

Blood smear, which is the gold standard diagnostic tool for malaria, needs to be repeated and the smear to be read by an experienced microscopist [10]. In some cases, diagnosis requires a placenta evaluation [11]. There is limited data about use of Rapid Diagnostic Test (RDT) in early malaria diagnosis. However, this diagnostic modality has been proven to be effective in adults' malaria diagnosis and there is no reason to think otherwise as far as neonatal malaria cases are concerned, though further research investigating the use of RDT in congenital malaria could be helpful.

Regarding the findings in lab investigations; Complete Blood Count (CBC), chemistry and glucose levels can help assess for complications of the [9], [11]

Management

The 2015 WHO guideline for management of malaria in neonates less than 5kg recommends the following [20]: to treat neonates weighing <5kg with uncomplicated Plasmodium Falciparum malaria with an Artemisinin-Combination Therapy (ACT) at the same mg/kg birth-weight target dose as for children weighing 5kg. This is a "strong recommendation" given by the WHO based on weak evidence as there is little in the current literature on the best treatment of congenital malaria.

The management of congenital malaria must always consider the parasites susceptibility pattern in the area. For Plasmodium Falciparum, the treatment with quinine for 5 days has yielded excellent results [8],[11],[21]. For other Plasmodium strains such as P. Vivax, P. Ovale; other protocols of malaria management are followed. It is also important to have in mind the potential for altered pharmacokinetics associated with prematurity [11]. Because congenital malaria is not apparent at its presentation, it is wise to consider and investigate for other diagnoses such as neonatal sepsis [9],[11].

CONCLUSION

Malaria is a significant cause of neonatal morbidity and mortality. Its presentation is a challenge in the early neonatal period because of its non-specific symptoms. This case series demonstrates that investigation and management is not standardized. WHO malaria guidance does not yet give specific guidance on investigating neonates exposed to intra-partum malaria. Our experience would suggest investigating these newborns with blood film analysis. This is especially important in neonates who have clinical manifestations of infection (e.g. fever) which might be otherwise falsely attributed to neonatal sepsis.

This case series is limited in its findings in that it is retrospective in nature and therefore we were not always able to obtain full information from the patients' files. Other challenges include the lack of full electronic record of the cases and the small number of exposed neonates. However, this is the nature of investigating a rare clinical entity.

Based on the findings of this paper we would recommend consensus work by the WHO or individual nations to develop guidance on how to best investigate, manage and follow-up neonates exposed to malaria during pregnancy.

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Table 1. Overview of the checked patients' files

Maternal malaria Case number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Malaria diagnosis in neonate	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No
Gestational age (weeks)	28	30	33	40	34	38	40	37	34	40	33	34	28	33	40	37	32
Antenatal care																	
Antenatal visits (number)	DNA	4	2	3	3	3	4	DNA	DNA	7	2	DNA	2	3	DNA	DNA	DNA
Maternal Malaria diagnosed in pregnancy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Antenatal steroids	Yes	No	Yes	No	Yes	No	DNA	No	No	No	Yes	Yes	DNA	Yes	No	No	No
Mode of delivery 1=SVD 2=Forceps 3=Vacuum 4=Elective cesarean 5=Emergency cesarean	1	1	5	5	5	5	5	5	5	1	1	5	1	1	1	1	5
Condition on arrival at NICU																	
Temperature	36.2	34.5	36.6	DNA	37.5	36.8	36.9	36.7	38.3	38.3	37	DNA	36.3	37	36	38.8	DNA
Suspected sepsis	Yes	Yes	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Suspected malaria	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	No
DOL at diagnosis	2	30	14	3													
Clinical signs of infection	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Investigations in the neonate																	
Blood culture	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CRP	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
FBC	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blood film	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	No
Blood film results	Pos	Pos	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg	NA	Neg	NA	Neg	NA	Neg	NA
Rapid Malaria Test	DNA	Yes	No	DNA	No	No	No	No	No	No	No	No	No	No	No	No	No
Treatment and outcomes																	
Antimalarial given	Yes	Yes	Yes	Yes	No	No	No	No	No	DNA	No	No	No	No	No	No	No
Number of days of antimalarial	4	10	2	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Outcome	Died	d/c	Died	d/c	d/c	d/c	d/c	d/c	d/c	d/c	d/c	d/c	d/c	d/c	d/c	d/c	Died
Length of admission (Days)	4	75	16	6	20	2	50	5	16	7	10	1	31	18	1	12	15

Table key: DNA = data not available. d/c = discharged, NA = Not applicable, DOL = day of life

REFERENCES

[1] S. A. Sotimehin, T. I. Runsewe-Abiodun, O. T. Oladapo, O. F. Njokanma, and D. M. Olanrewaju, "Possible risk factors for congenital malaria at a tertiary care hospital in Sagamu, Ogun State, South-West Nigeria," J. Trop. Pediatr., vol. 54, no. 5, pp. 313–320, 2008.

[2] C. C. Enweronu-Laryea et al., "Prevalence of congenital malaria in high-risk Ghanaian newborns: a cross-sectional study," Malar. J., vol. 12, no. 1, p. 17, 2013.

[3] J. Bukeyeneza, T. Rogo, E. Esmali, and A. Kanyamuhunga, "Malaria in Neonates: Case series," Rwanda Med. J., vol. 74, no. 4, pp. 13–15, 2017.

[4] CDC, "Congenital Malaria - Nassau County , New," 2017. [Online]. Available: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5415a3.htm. [Accessed: 01-Dec-2017].

[5] V. Kumar, J. C. Shearer, a Kumar, and G. L. Darmstadt, "Neonatal hypothermia in low resource settings: a review.," J. Perinatol., vol. 29, no. 6, pp. 401–412, 2009.

[6] S. Malviya and S. Shurin, "Case Report and Review: Intraerythrocytic parasites," Clin. Pediatr. (Phila)., vol. 23, no. 9, pp. 516–517, 1979.

[7] P. S. Kedar, K. Ghosh, R. B. Colah, and D. Mohanty, "Chronic persistent hemolysis in an infant: can we afford to forget malaria as a cause?," Hematol. J., vol. 3, no. 2, pp. 114–115, 2002.

[8] R. S. Gereige and D. Cimino, "Congenitally acquired chloroquine-resistant P. falciparum malaria in an infant born in the United States," Clin Pediatr, vol. 34, no. 3, pp. 166–169, 1995.

[9] A. I. Menasalvas Ruiz, A. Iborra Bendicho, J. L. Fuster, E. Cervantes

Hernández, and S. Alfayate Miguélez, "Unexplained Anemia in a Young Infant Due to Congenital Malaria," Pediatr. Infect. Dis. J., vol. 35, no. 4, p. 468, 2016.

[10] J. Stassijns, W. van den Boogaard, P. Pannus, A. Nkunzimana, and A. Rosanas-Urgell, "Prevalence and diagnostics of congenital malaria in rural Burundi, a cross-sectional study.," Malar. J., vol. 15, no. 1, p. 443, 2016.

[11] A. Ahmed, L. A. Cerilli, and P. J. Sanchez, "Congenital malaria in a preterm neonate: case report and review of the literature," Am J Perinatol, vol. 15, no. 1, pp. 19–22, 1998.

[12] V. Del Punta, M. Gulletta, A. Matteelli, V. Spinoni, A. Regazzoli, and F. Castelli, "Congenital Plasmodium vivax malaria mimicking neonatal sepsis: a case report.," Malar. J., vol. 9, p. 63, 2010.

[13] J. R. Poespoprodjo et al., "Case report: Severe congenital malaria acquired in utero," Am. J. Trop. Med. Hyg., vol. 82, no. 4, pp. 563–565, 2010.

[14] D. A. Opare, "Case Reports: Congenital Malaria In Newborn Twins," Ghana Med. J., vol. 46, no. 3, pp. 163–165, 2012.

[15] X. Liu et al., "A case of congenital plasmodium vivax malaria from a temperate region in central china," Malar. J., vol. 11, no. 1, p. 182, 2012.

[16] C. R. Lesko, P. M. Arguin, and R. D. Newman, "Congenital Malaria in the United States," Arch. Pediatr. Adolesc. Med., vol. 161, no. 11, p. 1062, 2007.

[17] J. G. Piñeros-Jiménez, G. Álvarez, A. Tobón, M. Arboleda, S. Carrero, and S. Blair, "Congenital malaria in Urabá, Colombia," Malar. J., vol. 10, no. 1, p. 239, 2011.

[18] K. Mohan and M. M. Maithani, "Congenital malaria due to chloroquine-resistant Plasmodium vivax: A case report," J. Trop. Pediatr., vol. 56, no. 6, pp. 454–455, 2010.

[19] G. Vottier, M. Arsac, C. Farnoux, P. Mariani-Kurkdjian, O. Baud, and Y. Aujard, "Congenital malaria in neonates: Two case reports and review of the literature," Acta Paediatr. Int. J. Paediatr., vol. 97, no. 4, pp. 505–508, 2008.

[20] World Health Organization, "Guidelines For The Treatment of Malaria," 2015.

[21] R. Viraraghavan, "Congenital Malaria : Diagnosis and Therapy Should Pediatric Hospitalists Replace the Staff / Ward Attending ?," Clin. Pediatr. (Phila)., vol. 39, no. 1, pp. 67–68, 2000.