**Long term sequelae of congenital gambiense Human African Trypanosomiasis**

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**Abstract**

*Background*

The clinical presentation of gambiense Human African Trypanosomias (gHAT) is generally considered the same among children and adults. In general, when describing the clinical presentation of children with gHAT, no differentiation is made between congenital gHAT and gHAT acquired later. There is a lack of knowledge regarding the signs and symptoms attributable to congenital gHAT and its long-term sequelae.

*Methods*

Following the evaluation of the hospital register of gHAT, the authors observed that six children born to mothers suffering from gHAT during their pregnancies still suffered from sequelae of the infection. The six mothers were interviewed about their respective pregnancies and the developmental history of the children borne to the infected mothers. Furthermore, the children then underwent a complete physical examination with a focus on neuropsychiatric signs and symptoms.

*Results*

Five of the six patients remain still seriously handicapped. Behavioral changes are present in four patients, tremor, speech impairment, involuntary movements, pathologic Baree Mingazini sign in three patients and convulsions, pyramidal signs, decreased muscle tonus in two patients. Two patients cannot work and one has a sphincter disorder.

*Conclusions*

Our study suggests that congenital gHAT may lead to long lasting sequelae in babies born from mothers treated after delivery. The risk of embryo toxicity of treatment of mothers with gHAT must be balanced out against the risk of congenital gHAT with long term sequelae.

**Keywords**: congenital HAT, long term sequelae, gHAT treatment during pregnancy, neuro-psychiatric signs

**Introduction**

The clinical presentation of *gambiense* Human African Trypanosomiasis (gHAT) is well described in adults. The disease evolves in two stages, the first or haemo-lymphatic stage and the second or meningo-encephalitic stage with trypanosomes invading the central nervous system [1].

The main symptoms of the first stage are fever, headache, pruritus, lymphadenopathy and, to a lesser extent, hepatosplenomegaly. The second stage is characterized by neuro-psychiatric signs and symptoms such as headache, mood or behavioral changes (irritability, aggressive behavior or inactivity with apathy or psychotic reactions), tremor, fasciculation, general motor weakness or complete paralysis, epilepsy, akinesia and abnormal movements (dyskinesia, choreoathetosis, Parkinson-like movements, unspecific movement disorders), speech disorders and abnormal archaic reflexes. Patients also suffer from sensory impairment (hyperaesthesia, paraesthesia, anaesthesia or pruritus) [2-7]. Cardiac involvement documented by electrocardiogram (ECG) alterations is observed in up to 70% of patients but rarely leads to relevant clinical heart failure [8, 9].

Children are usually considered to have the same symptoms as adults [4, 10-13]. . Amongst children, however, paresis was described in 8-27% [12, 14, 15], hemiparesis in 8-9% [5, 16], and malnutrition in up to 71% [14], whereas these manifestations are rarely observed in adults [6]. Cervical lymph node enlargement was significantly less frequent in very young children (<2 years old than in older children [13]. An unpublished analysis, performed in the context of a multinational drug utilization study (IMPAMEL II) [17], compared clinical signs and symptoms of 441 children below 15 years of age to those of 1944 adults: the incidence of fever, altered behavior and abnormal movements were significantly higher, but headache, pruritus and motor weakness was much lower in children (all p<0.05). However, these studies described the clinical presentation of children with gHAT in general and do not differentiate it from the signs and symptoms attributable to congenital gHAT.

The clinical presentation of congenital gHAT is limited to case reports and a small case series and no data on long-term follow-ups of these patients appears to be available. In this article, we describe the clinical presentation of six patients with congenital gHAT for whom follow up data for up to 21 years was available. Congenital infection is defined as the diagnosis of gHAT by detection of the parasite in a newborn of an infected mother within the first 5 days of life [18], or in children born outside an endemic country where tsetse (*Glossina*) transmission would not be possible. In addition probable, but uncertain congenital transmission can be assumed if the mother shows gHAT symptoms during the pregnancy and the newborn in the first five days after birth, but the diagnosis is only confirmed by detection of the parasite later than 5 days after birth. Recently, Welburn et al. [19] suggested that congenital transmission was much more frequent than had hitherto been considered and outlined the epidemiological evidence to support this view.

**Material and methods**

We describe an observational study carried out at the Hôpital Evangélique de Vanga (Vanga Health Zone (Kwilu Province) of the Democratic Republic of the Congo (DRC)) in January 2021.

In the frame of a study based on the hospital register of Vanga from 1999 to 2011, the mental health sequelae of stage two gHAT patients were evaluated. The register shows 869 cases of HAT including seven cases in pregnant women. Following this evaluation, the authors observed that children born to mothers suffering from gHAT during their pregnancies continued to suffer from sequelae of the disease after two decades. Six mothers were visited in their village and asked about the history of their pregnancy, their symptoms related to gHAT, the history of the newborns after the delivery, and about the development of the children from birth to the present day; the seventh mother - child pair could not be followed-up due to missing information about the pair in the register. As a second step, the children came for a complete clinical examination to Vanga Hospital. We conducted a complete physical examination with a focus on neuropsychiatric symptoms according to a standard case report form used in previous clinical HAT studies [20]. The quality of the earlier register information did not allow a systematic analysis of all children born to mothers suffering from gHAT during pregnancy in the Vanga hospital.

**Case descriptions**

Patient 1: 19 years old male

*History*

The patient presented the day after birth with convulsions, lethargy and inability to feed. Analysis of the cerebrospinal fluid (CSF) revealed the presence of trypanosomes in both, the mother and the child. The mother and the child were treated with three series of melarsoprol 3, 6 ml per kg i.v daily for three days with an interval of one week between the series shortly after delivery.

The child's growth and development was retarded. The mother reported that the child only started to stand upright at the age of 5 years and that her son could neither use his right arm nor his right leg. The child could not attend school because of a neuropsychiatric disorder.

*Physical examination*

At the age of 19, the patient’s body weight is 25 kg, the height 134 cm (BMI 14.1 kg/m2). He suffers from episodes of agitation, irritability, visible tremors and behavioral disturbances. He presents with a decreased strength for flexion and extension in his right arm and leg and is not able to walk unsupported.

Patient 2: 9 years old female

*History*

The diagnosis of gHAT in the mother was made almost at full term of her pregnancy. After delivery, the newborn presented with convulsions and a deviation of the mouth to the right side. As the mother had been diagnosed with gHAT, a lumbar puncture was carried out in the neonate immediately after delivery and revealed the presence of trypanosomes. The mother was treated with NECT (200 mg/kg of eflornithine as an intravenous infusion over 1–2 hours every 12 hours for 7 days combined with nifurtimox at 5 mg/kg orally every 8 hours for 10 days) and the girl was treated with eflornithine 150 mg/kg every 6 hours for 14 days. The girl developed normally apart from difficulties with holding objects with the left hand. She attends school and shows no neuropsychological or neurocognitive problems.

*Physical examination*

At the age of 9 years, the patient’s body weight is 28kg, the height 122 cm (BMI 18.8 kg/m2). We noticed a weakness of the tonus in the left arm and an inability to write. She can hold a fruit but has not enough force to throw it away.

Patient 3: 15 years old female

*History*

The pregnancy of the mother was reported to have been normal. Towards the end of the pregnancy, both parents were diagnosed with trypanosomiasis. The mother stayed at the hospital for treatment after delivery. The child was lethargic, refused to feed and did not cry after delivery. The lumbar puncture in the neonate revealed trypanosomes. During treatment, the child developed right hemiplegia, which gradually improved after physiotherapy. The mother later observed that the child had difficulty in hearing and could not speak. In addition, she observed epileptic seizures continuing until the present day and a primary amenorrhea. The mother and the child were treated with melarsoprol one series of 2.2 mg/kg per day in slow intravenous injections for 10 days within one month after the delivery.

*Physical examination*.

At the age of 15 years, the patient’s body weight is 16kg, the height 114 cm / (BMI 12.3 kg/m2 kg/m2). In the physical examination, the child shows behavioral disturbances (agitation, aggression) and an inability to hear or speak.

Patient 4: 21 years old male

*History*

The diagnosis of gHAT in the mother was made during the third month of pregnancy. The mother did not receive any treatment until delivery and her health status continued deteriorating. After delivery, the child presented with convulsions, feeding problems and incessant crying. The analysis of the CSF revealed the presence of trypanosomes. The mother and the child were treated with three series of melarsoprol 3, 6 ml per kg i.v daily for three days with an interval of one week between the series shortly after the delivery. The parents reported that the child was stunted. He started walking at the age of five. He continued to have seizures until he was about 10 years old. At present, seizures only occur rarely.

*Physical examination*.

At the age of 21 years, the patient’s body weight is 39 kg, the height 156cm. (BMI 16 kg/m2). He shows indifferent and incoherent behavior, sometimes with agitation, in combination with speech disturbance, presence of involuntary movements (athetosis) and weakness in both hands.

Patient 5: 13 years old female.

*History*.

The mother reported that the pregnancy was normal until delivery besides sleep disturbances, which were attributed to the pregnancy. The baby presented with strong tremors of his limbs. Within the first month after delivery, gHAT was diagnosed in both the mother and the newborn by detection of the parasite in the CSF. The mother and the child were treated with melarsoprol one series of 2.2 mg/kg per day in slow intravenous injections for 10 days within one month after the delivery. The child showed behavioral, language and marked learning deficits.

*Physical examination*.

At the age of 13, the patient’s weight is 31kg, the height 136 cm (BMI: 16.8 kg/m2). She is hyperactive, with visible tremor and abnormal movements of the arms like a repeated tic.

Patient 6: 20 years old male.

*History.*

Diagnosis and treatment of gHAT in the mother was made during the second trimester of pregnancy. At delivery, trypanosomes were detected in the blood and the CSF of the newborn. The parents do not report any problems with the child's growth. The child's development was normal and the child attended school without problems. He only mentions intermittent light to moderate headaches. The mother and the child were treated with three series of melarsoprol 3, 6 ml per kg i.v daily for three days with an interval of one week between the series shortly after delivery.

*Physical examination*.

At the age of 20, the patient’s weight is 50 kg, the height: 167 cm (BMI: 17.9 kg/m2). No abnormalities are found in the physical examination.

There was no report of a relapse or a reinfection with gHAT in all of the described patients.

**Discussion**

As far as we are aware, this is the first description of long-term sequelae of congenital trypanosomiasis. We describe a series of six children suffering from congenital gHAT, all of them diagnosed in the second stage. The diagnosis was based on the detection of trypanosomes in the CSF. In five of the children, the trypanosomes were detected within 5 days of delivery, in the sixth within one month. We included this child in the case series, since the mother was diagnosed with gHAT during the pregnancy and the first symptoms in the baby were observed within a few days after delivery. Given the hospital records and the age of the children at diagnosis, we conclude that transmission by *Glossina* can be ruled out.

Since 1993, only 18 cases of congenital gHAT, fulfilling the diagnostic criteria of either being diagnosed within 5 days after delivery or delivery in a non-endemic country [18], have been described in the literature [18, 21, 22]. Since one cluster of six cases [23] and the six cases described in this article were diagnosed in only two hospitals, the question arises if congenital gHAT is substantially underdiagnosed and/or underreported, even if the long-term sequelae are important and seriously impair the quality of life [19].

Long term sequelae 12-13 years after treatment, such as headache, neuropsychiatric symptoms and pruritus have recently been reported in adult gHAT patients [20]. In children younger than 15 years, observed 1-4 years after treatment of gHAT, nearly half had at least one sequela related to gHAT and 12% were seriously handicapped due to neurological and psychiatric problems including memory deficits, speech problems, convulsions or abnormal movements. Delayed psychomotor development and psychoneurotic disorders existed in 11.5% of the children [15]. In the current case series, the proportion of serious sequelae in congenital gHAT is much higher: Only one of the patient’s we report about had - apart from headache - no relevant sequelae. Five of the six patients are still seriously and probably permanently handicapped, even up to 20 years after birth. Behavioral changes remain present in four patients, tremor, speech impairment, involuntary movements, pathologic Baree Mingazini sign in three patients and convulsions, pyramidal signs, and decreased muscle tonus in two patients. Two patients cannot work and one has a sphincter disorder. In contrast to the American trypanosomiasis (Chagas disease), where late cardiac sequelae are often reported [8], none of the patients complained of cardiac symptoms. This concurs with observations in adults, where cardiac long-term- sequelae have not been observed [24].

In only one mother, the treatment was performed during the pregnancy in the second trimester. Of interest, her child developed also congenital gHAT despite the treatment of the mother but did not have long term sequelae. This case and the long term sequelae of children of mothers treated only after the delivery could be an argument for treating pregnant gHAT patients during pregnancy. However, the risk embryo toxicity of treatment of gHAT has be balanced out against the risk of congenital gHAT with long term sequelae.

**Limitations**

The precise number of pregnant women infected by gHAT cannot be determined in the register because female HAT patients were not systematically checked for pregnancy and some data could be lost. Therefore, the prevalence of congenital gHAT cannot be exactly determined. Similarly, the register did not allow us to distinguish between symptoms due to the disease and adverse events of treatment.

**Conclusions**

Our study shows that congenital gHAT was followed in five of six patients by long lasting sequelae, all in mothers not treated during pregnancy. The risk of embryo toxicity of treatment of gHAT has be balanced out against the risk of congenital gHAT with long term sequelae. However, whilst the majority of the patients in this study were treated with melarsoprol, with the well-known toxicity associated with the drug, improvements in treatment of gHAT over the last decades initially with the introduction of NECT and now the registration of the oral drug fexinidazole might provide an opportunity to review the treatment of pregnant patients. To date, with a decreasing incidence of gHAT, the awareness for the disease might decrease among medical staff [25]. Consequently, the diagnosis of gHAT in pregnant women and newborns might be increasingly unreported, leading to lifelong consequences for those borne by infected mothers. Continued public information and training of medical staff are necessary to maintain awareness of this disease. A systematic analysis of national and hospital registers of pregnant women with gHAT and their newborns with follow up of the newborns is warranted and essential for evaluating the true dimension of gHAT congenital transmission and for developing adequate preventive measures.

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**Conflict of Interest Statement.** The authors declare that they have no Conflict of Interest

**Author contribution:** JM and JB conceived the study; JM and JB designed the study protocol; JM carried out the clinical study, JM and JB drafted the manuscript; DHM and EK critically revised the manuscript for intellectual content and undertook editorial tasks. DHM and JB assisted in the application for funding. All authors read and approved the final manuscript. JM and JB are guarantors of the paper.

**Ethical Statement:** The study was approved by the “Comité National d’Ethique de la Santé “(CNES) (№ 228/CNES/BN/PMMF/2020) Kinshasa, République Démocratique du Congo. All participants or their legal guardians provided written informed consent prior to enrolment in the study.

**References**

1. Brun R, Blum J. Human African trypanosomiasis. Infect Dis Clin North Am. 2012;26(2):261-73. Epub 2012/05/29. doi: 10.1016/j.idc.2012.03.003. PubMed PMID: 22632638.

2. Kennedy PG. Human African trypanosomiasis-neurological aspects. J Neurol. 2006;253(4):411-6.

3. Antoine P. [Neurological and psychological studies of patients with sleeping sickness and their course]. Ann SocBelgMed Trop. 1977;57(4-5):227-48.

4. Ginoux PY, Frezil JL, Alary JC. [Symptoms of human trypanosomiasis at the first diagnostic phase in the People Republic of Congo (author's transl)]. Med Trop(Mars). 1982;42(3):281-7.

5. Edan G. [Clinical and biological symptoms of T. gambiense tryponosomiasis in the meningo-encephalitic period (author's transl)]. Med Trop(Mars). 1979;39(5):499-507.

6. Blum J, Schmid C, Burri C. Clinical aspects of 2541 patients with second stage human African trypanosomiasis. Acta Trop. 2006;97(1):55-64.

7. Bertrand E, Serie F, Kone I, Rive J, Compaore, Sentilhes L wet Philippe J, Symptomatologie générale de la trypanosomiase humaine africaine au moment du dépistage. Médecine d'Afrique Noire. 1973;20(4):303-14.

8. Blum JA, Zellweger MJ, Burri C, Hatz C. Cardiac involvement in African and American trypanosomiasis. Lancet InfectDis. 2008;8(10):631-41.

9. Blum JA, Burri C, Hatz C, Kazumba L, Mangoni P, Zellweger MJ. Sleeping hearts: the role of the heart in sleeping sickness (human African trypanosomiasis). Trop Med Int Health. 2007;12(12):1422-32.

10. Kazumba M, Kazadi K, Mulumba MP. [Characteristics of trypanosomiasis in children. Apropos of 19 case reports at the CNPP (Neuro-Psycho-Pathology Center), University Hospitals of Kinshasa, Zaire]. Ann SocBelgMed Trop. 1993;73(4):253-9.

11. Le Bras J, Sina G, Triolo N, Trova P. Symptomatology générale de la trypanosomiase humaine africaine de l'enfant. Med Trop (Mars). 1977;37(1):51-61.

12. Debroise A, Debroise-Ballereau C, Satge P, Rey M. [African trypanosomiasis in young children]. Arch FrPediatr. 1968;25(6):703-20.

13. Eperon G, Schmid C, Loutan L, Chappuis F. Clinical presentation and treatment outcome of sleeping sickness in Sudanese pre-school children. Acta Tropica. 2007;101(1):31-9.

14. Ngandu-Kabeya G. [Study of the symptomatology of African trypanosomiasis in children (apropos of 24 cases)]. Ann SocBelgMed Trop. 1976;56(2):85-93.

15. Cramet R. [Sleeping sickness in children and its long term after-effects. Apropos 110 personal observations at Fontem Hospital (Cameroon)]. Med Trop(Mars). 1982;42(1):27-31.

16. Giordano C, Clerc M, Doutriaux C, Doucet J, Nozais JP, Bureau JP, et al. [Neurological diagnosis at different stages of African trypanosomiasis in humans]. Ann SocBelgMed Trop. 1977;57(4-5):213-25.

17. Schmid C, Richer M, Bilenge CM, Josenando T, Chappuis F, Manthelot CR, et al. Effectiveness of a 10-Day Melarsoprol Schedule for the Treatment of Late-Stage Human African Trypanosomiasis: Confirmation from a Multinational Study (Impamel II). J InfectDis. 2005;191(11):1922-31.

18. Lindner AK, Priotto G. The Unknown Risk of Vertical Transmission in Sleeping Sickness-A Literature Review. Plos Neglected Tropical Diseases. 2010;4(12).

19. Welburn SC, Molyneux DH, Maudlin I. Beyond Tsetse--Implications for Research and Control of Human African Trypanosomiasis Epidemics. Trends Parasitol. 2016;32(3):230-41. Epub 2016/02/02. doi: 10.1016/j.pt.2015.11.008. PubMed PMID: 26826783.

20. Mudji J, Blum A, Grize L, Wampfler R, Ruf MT, Cnops L, et al. Gambiense Human African Trypanosomiasis Sequelae after Treatment: A Follow-Up Study 12 Years after Treatment. Trop Med Infect Dis. 2020;5(1). Epub 2020/01/17. doi: 10.3390/tropicalmed5010010. PubMed PMID: 31940846; PubMed Central PMCID: PMCPMC7157708.

21. De Kyvon MA, Maakaroun-Vermesse Z, Lanotte P, Priotto G, Perez-Simarro P, Guennoc AM, et al. Congenital Trypanosomiasis in Child Born in France to African Mother. Emerg Infect Dis. 2016;22(5):935-7. Epub 2016/04/19. doi: 10.3201/eid2205.160133. PubMed PMID: 27088460; PubMed Central PMCID: PMCPMC4861501.

22. Oba A, Gahtse A, Ekouya Bowassa G, Nika E, Obengui. [Congenital human African trypanosomiasis: an observation at the University Hospital of Brazzaville (Congo)]. Arch Pediatr. 2011;18(10):1114-5. Epub 2011/08/30. doi: 10.1016/j.arcped.2011.07.007. PubMed PMID: 21873039.

23. Triolo N, Trova P, Fusco C, Le Bras J. [Report on l7 years of studies of human African trypanosomiasis caused by T. gambiense in children 0-6 years of age]. Med Trop (Mars). 1985;45(3):251-7.

24. Blum A, Mudji J, Grize L, Burri C, Zellweger MJ, Blum J. Sleeping hearts: 12 years after a follow up study on cardiac findings due to sleeping sickness. One Health. 2020;11:100182. Epub 2021/01/05. doi: 10.1016/j.onehlt.2020.100182. PubMed PMID: 33392376; PubMed Central PMCID: PMCPMC7772621.

25. Mudji J, Benhamou J, Mwamba-Miaka E, Burri C, Blum J. The Flipside of Eradicating a Disease; Human African Trypanosomiasis in a Woman in Rural Democratic Republic of Congo: A Case Report. Trop Med Infect Dis. 2019;4(4). Epub 2019/12/15. doi: 10.3390/tropicalmed4040142. PubMed PMID: 31835660; PubMed Central PMCID: PMCPMC6958452.