Case Report: Magnetic Resonance Imaging Findings in Human African Trypanosomiasis: A Four-Year Follow-up Study in a Patient and Review of the Literature

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Abstract. Serial magnetic resonance imaging (MRI) was performed up to 4 years after treatment in a patient with Trypanosoma brucei gambiense infection. Four years after treatment and cure abnormalities were still present, although the patient led a normal social life, without physical and mental impairments. The literature on MRI in human African trypanosomiasis is reviewed. The MRI is useful to discriminate between encephalitis induced by trypanosomiasis and post-treatment reactive encephalopathy, a severe and often fatal complication of treatment, in particular of treatment with arslenicals. The MRI is not useful for diagnosis of human African trypanosomiasis (HAT).

INTRODUCTION

Human African trypanosomiasis (HAT) is caused by the protozoan parasite Trypanosoma brucei gambiense in West and Central Africa and by Trypanosoma brucei rhodesiense in East Africa. Trypanosomiasis is characterized by two stages, the first of hemolymphatic involvement, the second of central nervous system (CNS) invasion, West African trypanosomiasis (WAT) is a chronic disease with progression over months, even years to the final CNS stage of complete lethargy, coma, and death. The parasite is transmitted by tsetse flies, man is the reservoir. East African trypanosomiasis (EAT) is an acute disease with involvement of the CNS within days to weeks after the infective tsetse bite; without treatment death will follow within a few months. East African trypanosomiasis is a zoonosis with antelopes and cattle as reservoir. In 2004, 17,000 new cases of T.b. gambiense infection and 580 of T.b. rhodesiense infection were reported in endemic countries.1 About 20 T.b. gambiense and 30 T.b. rhodesiense infections are diagnosed yearly outside Africa.2 The diagnosis of trypanosomiasis is definite by finding the parasite in blood, lymphnodes and, in CNS involvement, in the cerebrospinal fluid (CSF). In any patient with trypanosomiasis the CSF must be examined to exclude CNS involvement because of a difference in treatment and prognosis.

Magnetic resonance imaging (MRI) is not readily available in countries where trypanosomiasis is endemic, thus systematic MRI studies are not available. In case reports of patients treated in non-endemic countries MRI results are described. In these patients, MRI was generally performed during active infection and treatment and relatively shortly after treatment. Long-term follow-up studies are lacking. We report MRI findings in a patient with West African trypanosomiasis up to 4 years after recovery.

CASE REPORT

A 27-year-old female refugee from Angola was admitted to a regional hospital because of fatigue, apathy, sleepiness, loss of appetite, and depression. She had arrived in The Netherlands since 2 years before and had not left the country. On admission no abnormalities were detected at physical examination and no paralysis was present. A computed tomography (CT) scan of the brain was normal. At the suggestion of the family who knew trypanosomiasis from their native village, serology for trypanosomiasis was performed. The enzyme-linked immunosorbent assay (ELISA) IgG titer was 1:200, a positive result. As the titer remained the same at repeat testing, it was concluded that this was not consistent with an active infection. No diagnosis was made. During a second admission 6 months later, T2-weighted and fluid-attenuated inversion recovery (FLAIR) MR images of the brain revealed symmetric, confluent hyperintense signal of the supratentorial white matter and to a lesser extent also of the basal nuclei. A definite diagnosis could not be made but progressive multifocal leukoencephalopathy (PML) was considered. At a third admission, 2 months later, the attending neurologist asked advice by telephone at our center and within hours the diagnosis West African trypanosomiasis with CNS involvement was established by demonstration of the parasite in CSF. The patient was transferred to our hospital for treatment. The CSF IgM levels were increased to 277 μg/L and the white cell count was 74/μL. The ELISA IgG titer in serum was 1:200, as before. On admission into our hospital, the consciousness of the patient was severely depressed. She opened her eyes at painful stimuli, but showed no verbal reactions. Motor response was limited to flexion on painful stimulation of the right arm (Glasgow coma score E2, V1, M 4). The face was swollen and there was a bite wound in the left lower lip. There was a gaze deviation to the right and left-sided spasticity of the arm flexors. Tendon reflexes were brisker on the left; plantar reflexes showed a left flexor response, and no response on the right side. During the examination an episode of repeated contractions of the left arm with more extreme right gaze deviation occurred, which was interpreted as a focal seizure. She was treated with eflornithine during 14 days and with valproate because of seizures. The T2-weighted and FLAIR MR images, 14 days after end of treatment (Figure 1), showed a bilateral hyperintense signal of the supratentorial white matter extending to the right basal nuclei and mesencephalon and a vague perivascular enhancement near the right basal nuclei. These findings were more pronounced in the right than in the left hemisphere and comparable with those of the MRI performed in the regional hospital before referral.

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She recovered slowly but steadily and 4 weeks after the end of treatment she was transferred to a rehabilitation center. Nine months after treatment MRI showed minor improvement (Figure 2A and B), although the patient had improved considerably, both physically and mentally. Two years after treatment MRI had significantly improved (Figure 3A and B), but the hyperintense signal on T2-weighted and FLAIR MR images in the corona radiata and the right semi-oval center and right basal nuclei still persisted. Some dilatation of the right lateral ventricle was present indicating brain atrophy. A final MRI was made 4 years after treatment when the patient had fully recovered and was living a normal social life. The MRI showed only remnants of the T2-hypersignal in the white matter. In the right hemisphere some localized periventricular T2-hyperintensities were still present. In the left hemisphere and in the basal nuclei only a minimally hyperintense signal remained. As before, the right lateral ventricle was enlarged consistent with brain tissue loss (Figure 4A and B).

**MRI REPORTS IN HAT PATIENTS: REVIEW OF THE LITERATURE**

The first report on MRI in HAT was probably in a letter to *Lancet*. An 18-year-old Angolan woman was diagnosed with HAT 18 months after her arrival in Italy. The MRI showed a high intensity signal in the frontal and medial temporal white matter, suggesting leukoencephalitis. Eight months after treatment MRI showed reduction of the high intensity signal. At that time the patient was symptom free. In addition, we found seven case reports, three about patients with WAT and four patients with EAT.

All three patients with WAT were originally from endemic countries. One was from Equatorial Guinea and was diagnosed in Spain, the other two were from the Democratic Republic of Congo, diagnosed in France and Canada, respectively. The latter patient was described in two articles, one of which specifically reports on MRI findings. The complaints of these patients started about 15, 21, and 24 months after immigration into the non-endemic country. Diagnosis was established around 4, 6, and 9 months, even 4 years later, so at least 6 years after departure from the endemic area. Two patients presented with a psychiatric illness. The MRI revealed bilateral, hypointense abnormalities in the white matter on T2-weighted images in all three, in one patient also of the basal nuclei.
brainstem, oval centers, red nuclei, substantia nigra, and mesencephalon, and in another also in the external and extreme capsule, in basal ganglia, and midbrain. In the third patient a low intensity signal in thalami, locus niger, red nuclei, and anterior quadrigemini tubercles was observed. The MRI after treatment showed improvement in all three. In one patient, only a light hyperintense signal in the oval centers remained one week after end of treatment. In another patient, the MRI at 18 months after treatment showed diffuse cortical and subcortical atrophy and partial regression of the T2 high-intensity signal in the white matter of semi-oval centers, but persistence of high intensity signal of white matter in the frontal horns and of the symmetric low intensity signal of the basal ganglia. Moderate ventricular enlargement indicative of white matter loss with a decrease of high intensity signal in the basal ganglia was noted in the third patient, one year after treatment.

The four patients with EAT were all tourists who respectively visited Rwanda, Tanzania, Kenya, Tanzania, and several southern African countries (Namibia, Mozambique, Malawi, and South Africa). Diagnosis of EAT was established.
15 days to 6 weeks after exposure in three patients, in one after 4 months. In one patient MRI was performed just before or at the beginning of treatment (not clear from the report), about 6 weeks after the infective bite while the patient was symptomatic since 4 weeks. This MRI showed only meningeal thickening. In this patient, MRI was repeated because of deterioration during treatment with melarsoprol. The T2-weighted images then revealed a symmetrical high signal in the posterior limb of both internal capsules, middle cerebellar peduncles, and the splenium of the corpus callosum. Meningeal thickening had regressed and brain oedema and focal lesions were not noted. Melarsoprol was continued and the patient recovered. One year later MRI showed small residual lesions in the left cerebellum but all other lesions had disappeared.

In the other three patients MRI was performed because of complications during or after treatment. In the 38-year-old British patient who visited several southern African countries, the first MRI performed at the time of a second relapse showed demyelination near the right lateral ventricle. During treatment with melarsoprol, together with prednisolone, the patient developed generalized tonic-clonic seizures. The MRI revealed widespread bilateral T2-weighted hyperintensities in the supratentorial and infratentorial white matter and multiple microhemorrhages suggesting a complication of treatment, the so-called post-treatment reactive encephalopathy (PTRE). Melarsoprol treatment was interrupted and prednisolone was continued. The MRI about 5 weeks later demonstrated considerable resolution of the white matter changes, with persistent microhemorrhages. Thereafter, the melarsoprol course was resumed and completed. The patient recovered but with sequelae of a pyramidal syndrome and cognitive impairment. A 62-year-old American woman who had visited Kenya and Tanzania, developed paresthesias, an ataxic gait and brisk reflexes 4 weeks after treatment with suramin and melarsoprol with prednisolone for EAT. The MRI showed multiple enhancing areas of increased T2 signal in the central gray matter and cortex on T2-weighted images then revealed a symmetrical high signal in the posterior limb of both internal capsules, middle cerebellar peduncles, and the splenium of the corpus callosum. Meningeal thickening had regressed and brain oedema and focal lesions were not noted. Melarsoprol was continued and the patient recovered. One year later MRI showed small residual lesions in the left cerebellum but all other lesions had disappeared.

The reported abnormalities of MRI are not typical for sleeping sickness and can be found in patients with a diagnosis of leuкоencephalitis, PML, cerebral gliomatosis, acute demyelinating encephalomyelitis (ADEM), adenoleukodystrophy, metachromatic leukodystrophy while also lymphoma and tuberculosis are suggested. A radiologist confronted with these MRI findings will have to consider trypanosomiasis as well. Once a diagnosis of HAT is established, there is no need to perform MRI studies but MRI becomes very helpful if these MRI findings will have to consider trypanosomiasis as well. The diagnosis of HAT, sleeping sickness, is established by demonstration of the parasite in blood, a lymphnode aspirate, or CSF. Indirect evidence can be obtained by serologic tests detecting antibodies from about 3 to 4 weeks after infection. There is no universal consensus on the CNS findings defining late-stage HAT. A white blood cell count > 10/μL and/or increased IgM levels in CSF are mentioned but total protein measurement for staging HAT is no longer recommended. The CNS involvement is confirmed by finding the parasite in CSF. The MRI does not play a role for the diagnosis. The MRI findings in patients with HAT may vary from meningeal thickening in early disease to bilateral confluent hyperintensive T2 signal of supratentorial white matter, brainstem, and cerebellum later in the course of disease. The ventricular enlargement apparent in MRI studies in our patient from 9 months after treatment and recovery is consistent with brain loss. Brain atrophy, as seen on MRI, has been reported before and might be a result of the perivascular infiltration and encephalitis described in these patients. Atrophy and brain loss are not normally described in the pathology of trypanosomiasis. We suggest that this may occur late after recovery and that it is MRI that makes this visible. Pathology studies are performed on patients who died during active disease and treatment when this supposedly late effect may not yet have developed.

DISCUSSION

Trypanosomes were not detected in the CSF, the white blood cell count in the CSF was 2/μL and the protein level had decreased from 1.13 g/L to 0.76 g/L. It was concluded that HAT encephalitis had been treated adequately and treatment was not resumed. One week later the electroencephalogram (EEG) was almost flat and the MRI showed worsening of the encephalitis but no hemosiderin deposits, commonly seen in arsenic encephalopathy and indicating earlier hemorrhage (PTRE). The patient died and autopsy showed widespread lymphoplasmacytic perivascular inflammation in the brainstem, cerebellum, and cerebrum. The most extensive foci of inflammation were present in the cerebral white matter with demyelination and axonal damage. Hemorrhages were not found. These findings were concordant with what was demonstrated by MRI. The details of all patients are summarized in Table 1.
leukoencephalopathy was found in the thalamus and brainstem, with fibrinous necrosis of small blood vessels. In active HAT-induced encephalitis, MRI is characterized by a bilateral confluent hyperintense signal of the white matter. Usually, the internal capsules, basal ganglia, and cerebellum are affected. The gray matter seems less frequently affected. Microscopically, a widespread perivascular meningoencephalitis with glial proliferation and sparing of the neuronal elements is revealed. Oedema does not occur and demyelination occurs only late in the disease. Distinction between the two conditions is important, as in PTRE melarsoprol treatment should be stopped and high dose corticosteroids should be started, whereas in HAT encephalitis specific treatment should be continued.

Only a few reports about MRI during long-term follow-up of HAT patients are available. We could follow our patient up to 4 years after treatment and observe that the regression of abnormalities lagged behind recovery. Two years after treatment, when the patient had already fully recovered, significant white matter abnormalities were still present. Four years after treatment discrete remnants of these white matter abnormalities still remained.

### REFERENCES


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**Table 1**

<table>
<thead>
<tr>
<th>Author and others</th>
<th>Time delay diagnosis: clinical symptoms; outcome</th>
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<th>MRI findings</th>
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<tr>
<td>Serrano-Gonzalez and others</td>
<td>T delay –30 months; headache, disturbance of consciousness and sleep; psychiatric disorders; recovered</td>
<td>Serum: elevated IgM, serology negative trypanosomes in CSF</td>
<td>Bilateral HIS extending into basal and red nuclei and into substantia nigra</td>
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<tr>
<td>Bedat-Millet and others</td>
<td>T delay –6 years; hepatosplenomegaly psychiatric disorders since 4 years; recovered with sequelae; psychomotor disturbances and tremors</td>
<td>Serum: HA1 1:128, CSF IFA 1:4 (pos) trypanosomes in blood</td>
<td>Bilateral and cerebellar HIS</td>
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<tr>
<td>Sahlas and others</td>
<td>T delay –19 months; psychiatric disorders; posterior cervical lymphadenopathy; extrapyramidal signs; hyperesthesia; recovered (sequelae: sleep disturbances)</td>
<td>Serum: IgM elevated, CSF: WBC 342/mm³, protein 105 mg/dL; trypanosomes in blood/CSF</td>
<td>Bilateral HIS in gray and white matter and in basal ganglia</td>
</tr>
<tr>
<td>Sabah and others</td>
<td>T delay –1 month; headache, weight loss, fever, purpura, hepatosplenomegaly, lymphadenopathy; recovered (sequelae: bilateral palomental reflex)</td>
<td>“CSF involvement” (data not specified), trypanosomes in blood and bone marrow</td>
<td>Thickening of meninges; PTRE as a complication of melarsoprol therapy</td>
</tr>
<tr>
<td>Braakman and others</td>
<td>T delay –15 days; fever, headache, drowsiness, tremors, organic psychosyndrome; relapse? PTRE? died</td>
<td>CSF: WBC 83/μL, protein 191 mg/dL; trypanosomes in blood/CSF</td>
<td>Bilateral HIS in gray and white matter</td>
</tr>
<tr>
<td>Kumar and others</td>
<td>T delay –4 weeks; fever, rash, no neurological symptoms; multifocal inflammatory leukoencephalopathy; recovered</td>
<td>CSF: WBC 164/μL, protein 191 mg/dL; trypanosomes in blood</td>
<td>HIS in cervical spine, cerebellum, brainstem, and in subcortical white matter</td>
</tr>
<tr>
<td>Checkley and others</td>
<td>T delay –4 months (?); fever, headache, sleeplessness; posterior cervical and axillary lymphadenopathy, hepatomegaly; relapsed twice; recovered with remnant pyramidal syndrome and cognitive impairment</td>
<td>CSF: WBC 82/μL, protein 1.2 g/L; trypanosomes in blood</td>
<td>HIS in supratentorial and infratentorial white matter; multiple microhemorrhages (PTRE)</td>
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<tr>
<td>Present work Angola</td>
<td>T delay &gt;2 1/2 years; apathy, sleeplessness, depressed consciousness; recovered</td>
<td>Serum: ELISA 1:200; CSF: IgM 277 mg/L, WBC 74/μL; trypanosomes in CSF</td>
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<td>Spinazzola and others</td>
<td>T delay –18 months; fever, ataxia, tremors, hepatomegaly; recovered</td>
<td>Serum: IHAT 1:1024 CSF: 1:8 trypanosomes in blood/CSF</td>
<td>HIS in frontal and temporal white matter</td>
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<tr>
<td>Gill and others</td>
<td>T delay ~4 months (?); fever, rash, lymphadenopathy, hepatomegaly; recovered</td>
<td>Serum: ELISA 1:4; CSF: IgM 35 mg/L, WBC 82/μL, protein 0.85 g/L; trypanosomes in blood/CSF</td>
<td>CT in frontal and temporal white matter</td>
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<tr>
<td>Bhat and others</td>
<td>T delay ~10 months; ataxia, tremors, hepatomegaly; recovered</td>
<td>Serum: IgM elevated, CSF: WBC 342/mm³, protein 105 mg/dL; trypanosomes in blood/CSF</td>
<td>Bilateral HIS in gray and white matter and in basal ganglia</td>
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*IHAT = human African trypanosomiasis; MRI = magnetic resonance imaging; WAT = West African trypanosomiasis; IHAT = immune haemagglutination test; CSF = cerebrospinal fluid; PTRE = post-treatment reactive encephalopathy; HIS = haemagglutination inhibition; IFA = immunofluorescence assay; WBC = white blood cell count; EAT = East African trypanosomiasis; ELISA = enzyme-linked immunosorbent assay.*


