STAGE DETERMINATION AND FOLLOW-UP IN SLEEPING SICKNESS

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ABSTRACT • In order to select a correct treatment after primary diagnosis of trypanosomiasis infection, accurate assessment of the disease stage, haemo-lymphatic or meningo-encephalitic, is essential. This is achieved by lumbar puncture and subsequent examination of the cerebrospinal fluid. These examinations have to be repeated during 2 years after treatment, and only after the cerebrospinal fluid has normalized one can decide on complete cure. The currently used cerebrospinal fluid parameters, i.e. white blood cell count, total protein determination and finding of trypanosomes, and practical problems encountered using these parameters are discussed. Alternative markers for stage determination and follow-up include trypanosome specific antibodies, anti-galactocerebroside antibodies and IgM measurement in CSF.

KEYWORDS • Human African trypanosomiasis - Meningo-encephalitic stage - Cerebrospinal fluid - Diagnosis - Cell count - Protein - Trypanosome detection - Antibody - IgM.

DETERMINATION DU STADE ET SUIVI APRES TRAITEMENT DANS LA TRYPANOSOMIASE HUMAINE AFRICAINE

RESUME • Pour sélectionner le traitement approprié après un diagnostic de la trypanosomiase humaine africaine, il est essentiel de déterminer correctement le stade de la maladie, lymphatico-sanguin ou méningo-encéphalitique. La détermination du stade est réalisée par l'analyse du liquide céphalo-rachidien, obtenu par ponction lombaire. Les examens doivent être répétés pendant 2 ans après traitement, et un patient est déclaré guéri seulement après la normalisation de son liquide céphalo-rachidien. Les paramètres actuellement utilisés, numération des globules blancs, détermination de la protéinorachie et recherche des trypanosomes dans le liquide céphalo-rachidien, et les problèmes pratiques associés sont discutés. Les marqueurs alternatifs pour la détermination du stade et pour le suivi après traitement sont les anticorps spécifiques de trypanosomes, les anticorps anti-galactocérébrosides et le taux d'IgM dans le liquide céphalo-rachidien.

MOTS-CLES • Trypanosomiase humaine africaine - Stade méningo-encéphalitique - Liquide céphalo-rachidien - Diagnostic - Cytorachie - Protéinorachie - Recherche de trypanosomes - Anticorps - IgM.

The disease course of Human African Trypanosomiasis caused by infection with *Trypanosoma brucei gambiense* or *rhodesiense* evolves in 2 periods (1, 2). The haemo-lymphatic period or first stage is characterized by dissemination and subsequent proliferation of trypanosomes in blood, lymph and other tissues. The second or meningo-encephalitic stage, appearing after weeks in *Trypanosoma brucei rhodesiense* infections and after months or years in *gambiense* infections, is caused by trypanosome invasion into the central nervous system.

Accurate assessment of the disease stage is essential in order to select the optimal treatment with minimal risk for the patient. The relatively safe drugs used for first stage treatment are inefficient in the second stage since they do not sufficiently cross the blood-brain barrier. Melarsoprol, the drug almost exclusively used for second stage treatment is highly toxic and in up to 5 % of the patients a treatment associated encephalitic reaction occurs which is often fatal (3, 4). Since there is no exclusive clinical sign indicating the evolution from the haemo-lymphatic to the meningo-encephalitic period, stage determination is done by examination of the cerebrospinal fluid (CSF), which is obtained by lumbar puncture (Fig. 1).

In order to be sure of complete cure, the CSF should be re-examined repetitively during two years after treatment (5). A patient can only be considered cured 2 years after therapy, if no trypanosomes can be found in blood, lymph and CSF, if he is clinically well and if the CSF has returned to « normal ».

In comparison to other infections affecting the central nervous system, only few tools for determining nervous system involvement in sleeping sickness and for follow-up after treatment exist. Even fewer are the tools applicable in

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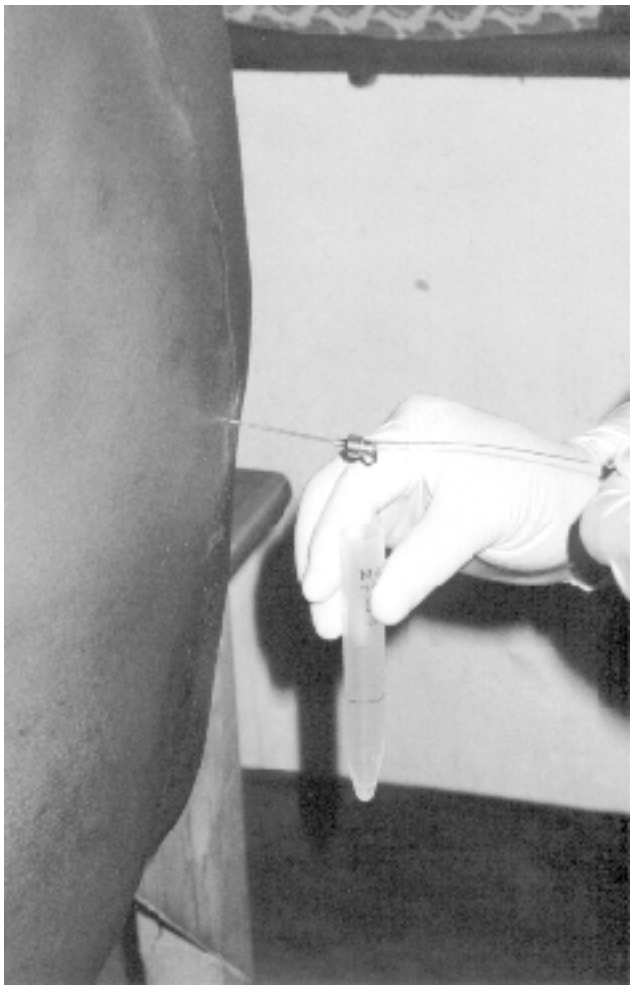

Figure 1 - Sampling of cerebrospinal fluid by lumbar puncture.

Figure 2 - Execution of the cell count.

rural control centers in endemic areas, and often they are suboptimally used. This review discusses the meaning of CSF parameters used for stage determination and follow-up, practical problems encountered and innovative tools with emphasis on applicability in the field.

Following the WHO recommendations for stage determination and follow-up (5), the CSF has to be examined on white blood cell number, total protein concentration and presence of trypanosomes. Alternative markers for stage determination and follow-up include trypanosome specific antibodies, anti-galactocerebroside antibodies and IgM measurement in CSF.

EXAMINATION OF CSF : PARAMETERS PRESCRIBED BY WHO

CSF cell count.

CSF white blood cell count is the most widely used technique for stage determination and follow-up (Fig 2). Counting chambers particularly suited to execute the CSF white blood cell count are the Fuchs-Rosenthal, Neubauer or Malassez counting chamber. The CSF is used undiluted, since addition of for example Türck solution will not only lyse red blood cells, but also trypanosomes that might be present in CSF. The «normal» upper limit for CSF cell number has been set arbitrarily to 5 cells/µl but should be interpreted with caution.

Based on biological disturbances in the CSF of sleeping sickness patients, it has already been suggested to raise the cut-off to 20 cells/µl (6). Patients with up to 20 cells/µl in their CSF have been successfully treated with pentamidine (7). On the other hand, a considerable amount of relapses has been observed in a clinical study carried out in Uganda when patients with 5-20 cells/µl in the CSF were treated with pentamidine (Legros 1998, personal communication).

Concurrent infections such as HIV, inducing pleocytosis in CSF may complicate the interpretation of cell counting results before and after treatment. This arguments against the conclusion of Miézan et al. (8) who state that in poorly equipped laboratories, the diagnosis of CNS involvement in patients with confirmed systemic infection can be based on the white cell count only.

Although cell count is often the only parameter checked, only few guidelines can be found for follow-up. Pépin & Milord (3) consider cell counts higher than the previous determination and above 50 cells/µl as a relapse, even if the patient is asymptomatic. Cell counts higher than the previous one and between 20 and 49 cells/µl, are only considered as relapse when symptoms recur. When the cell count is high (>50 cells/µl), but lower than the previous one, they recommend not to treat as it can take months before the cell count returns to normal. It is also known that there can be a significant increase in CSF cell number immediately after melarsoprol treatment, which is not at all predictive of relapse. A significant increase in cell number compared to previous controls, even in the absence of trypanosomes, is indicative for treatment failure according to the guidelines of the *Bureau Central de la Trypanosomiase* in DR Congo (9).

Trypanosome detection in CSF.

The finding of trypanosomes in CSF allows immediate classification of a patient in meningo-encephalitic stage. When the number of parasites in the CSF is very high, trypanosomes can be detected during white blood cell count. In case of low trypanosome numbers, parasites can be concentrated by centrifugation of a larger volume of CSF, followed by transfer of the sediment on a slide for microscopic examination (10). To improve trypanosome detection, double centrifugation of CSF has been introduced (11). Recently, a modified single centrifugation technique has been introduced which is a simple, sensitive, rapid and cheap alternative to double centrifugation (12).

For maximal sensitivity, CSF should be centrifuged immediately after lumbar puncture, because trypanosomes in CSF seem to be more fragile than those in blood and start to immobilize and lyse within 10 minutes (13).

The meaning for stage determination of low numbers of trypanosomes, in otherwise normal CSF, is not clear. Using the double centrifugation technique, Cattand (in 12) observed that 22 % from the patients with normal protein concentration and cell number turned out to have trypanosomes in CSF. Using *in vitro* culture, trypanosomes were found in CSF of 54 % of patients with normal protein concentration and cell number (8). Successful treatment with pentamidine of such patients has been achieved (7). Therefore, the meaning of the presence of trypanosomes in CSF for stage determination, and the hypothesis that these patients could be cured with first stage drugs, remains to be investigated. Detection of trypanosomes in CSF during the follow-up period however, leaves no doubt of treatment failure. Therefore, the use of the most sensitive techniques is recommended during follow-up, especially when other CSF parameters remain abnormal or when clinical signs for nervous system involvement are present.

Determination of csf protein concentration.

Probably due to the need of a spectrophotometer, the instability of the reagents, and the belief that CSF protein concentration is correlated with CSF cell number and adds no additional information, protein quantification is not a current practice in sleeping sickness control centers. An elevated protein content can however be an indicator of serious central nervous system involvement such as blood-brain-barrier impairment (6, 14-16) or astrocyte activation and neurodegeneration (17).

A wide variety in protein quantification methods for CSF is available : precipitation methods with sulfosalicylic acid or trichloroacetic acid (18), or colorimetric methods such as the the Coomassie brilliant blue method (19, 20) or the BCA method (21). Advantages of precipitation methods are their simplicity and the use of relatively cheap and currently available reagents. They can therefore easily be performed when only limited technical equipment and a larger volume of CSF are available. For research use, when usually small amounts of CSF are available, the dye binding method and BCA method are more suited. Different results may however be obtained depending on the method applied and on the protein standard used (22) and therefore, largely differing cut-off values can be found (23) ; 250 mg/l (trichloroacetic acid precipitation), 370 mg/l (Coomassie brilliant blue method) or 450 mg/l (sulfosalicylic acid precipitation). It is recommended, when choosing a method, to determine an «in house» cut-off for that method by testing a series of normal CSF samples.

OTHER USEFUL PARAMETERS FOR STAGE DETERMINATION

Trypanosome specific antibodies in CSF.

The detection of trypanosome specific antibodies in CSF of second stage patients by indirect immunofluorescence and ELISA has been described extensively (14, 24-29). Furthermore, by ELISA it is possible to separately and semi-quantitatively study different immunoglobulin classes and isotypes in serum and CSF. This allows the calculation of intrathecal synthesis of specific antibodies, indicating an inflammatory response in the central nervous system (15, 16).

The possibility to detect trypanosome specific antibodies in CSF by techniques applicable on the field such as CATT, indirect immunofluorescence and indirect haemagglutination has been explored by Lemesre et al. (30). They concluded that, due to its low sensitivity, CATT was not suited to detect antibodies in CSF whereas indirect haemagglutination presented the highest sensitivity and specificity. LATEX/*T.b. gambiense* can also be performed on CSF samples, allowing the detection of trypanosome specific antibodies in CSF. The reagent seems not to be 100 % sensitive, but is highly specific for second stage trypanosomiasis (31). A disadvantage of indirect agglutination is that it does not allow the differentiation between IgG and IgM, unlike ELISA.

It has been described that CSF antibodies drop down quickly after successful treatment (27-29). The decrease of

trypanosome specific antibodies concentrations in CSF could therefore be a good parameter for definite cure.

Anti-galactocerebrosides.

Antibodies directed against brain specific proteins have been detected in serum and CSF of sleeping sickness patients. Anti-galactocerebrosides can be detected by ELISA in CSF of second stage sleeping sickness patients as a marker for central nervous system involvement (32-34). Further studies on the anti-galC ELISA for stage determination and its adaptation into a simpler test are however necessary before implementation into the field. No data are available yet on evolution of these antibodies during follow-up.

IgM concentration in cerebrospinal fluid.

It has been known for long that the CSF of second stage sleeping sickness patients can contain high levels of IgM. An increased IgM concentration in CSF is therefore a marker of interest for determination of the second disease stage in sleeping sickness (14, 16, 26, 28, 35, 36,). Due to its size, IgM does not pass a normally functioning blood-brain barrier and normal concentrations in CSF are extremely low (37). The presence of high levels of IgM in CSF of sleeping sickness patients can therefore only be explained by a leaking blood-brain barrier or by intrathecal synthesis, both indicators of inflammation in the central nervous system.

IgM in CSF can be determined by classical nephelometric methods. Probably due to the lack of appropriate techniques to quantify IgM in CSF under field situations, IgM determination is however seldom used for stage determination. Therefore we developed a latex agglutination test (LATEX/IgM), which combines stability, sensitivity and simplicity (38). The test is under evaluation in different control centers.

However, one should keep in mind that IgM in CSF is only indicative for second stage trypanosomiasis when the CSF has not been contaminated with blood during lumbar puncture since even small volumes of blood give a strong rise of IgM in CSF (39).

Reports on the evolution of IgM levels after treatment are contradictory. According to Knobloch et al. (28), efficacy of treatment is indicated by a decrease of IgM in CSF, and levels of IgM could return to normal after weeks or months (36). On the other hand, Whittle et al. (26) describe a slow decrease of IgM in CSF up to one year after treatment. At that moment however, relapses would be characterized by high CSF IgM (26, 40), whereas the absence of IgM in CSF even with high protein and cell number should cast doubt about diagnosis of relapse.

AN OVERVIEW OF RESEARCH ACTIVITIES ON STAGE DETERMINATION

In addition to the parameters already discussed, other markers for central nervous system involvement have been studied. Inflammation related markers include blood-brain barrier impairment (6, 15, 16), immune complexes in CSF (14), prostaglandins in CSF (41), nitric oxide (42, 43) and cytokines and anti-cytokine autoantibodies (43-45). All these parameters indicate mainly the occurrence of inflammatory reactions and are therefore not necessarily sleeping sickness specific. Furthermore, they may reflect events going on in other body compartments than the CNS. Among the «brain specific» markers are antibodies against brain proteins such as myelin and neurofilament (46-48) or brain proteins such as glial fibrillary acidic protein and neurofilament (17, 49). As for inflammation related parameters, none of these parameters is exclusively trypanosomiasis specific. «Trypanosome related» markers include trypanosomal antigens in CSF (50, 51), TLTF and anti-TLTF (52) and trypanosome nucleic acid in CSF (53, 54, 55). Although being disease specific, these parameters have the disadvantage of not necessarily originating exclusively from the central nervous system.

All these markers merit further investigation. Furthermore, they should be evaluated in view of their application in stage determination and follow-up in sleeping sickness. Some of them, particularly antibody detection tests, could relatively easily be adapted to field tests ■

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Jean-Paul Bado

Médecine coloniale et grandes endémies en Afrique

A la fin du XIX^{e} siècle, l'Europe, qui connaît une grande expansion, mène en Afrique des guerres de conquête. A la même époque, la médecine occidentale est en plein essor avec l'usage croissant du microscope et les découvertes de Pasteur, de ses devanciers et de ses rivaux.
La situation sanitaire en Afrique conquise est déplorable. Elle va s'aggraver avec les bouleversements induits par la colonisation : déplacements de population, travail forcé, traite commerciale... L'administration coloniale s'attaque en priorité à la variole et au paludisme, maladies meurtrières certes, mais elle occulte les ravages que font la lèpre, la maladie du sommeil et l'onchocercose, en AOF notamment. L'auteur s'attache particulièrement à ces trois grandes endémies. Pourquoi les structures de prophylaxie contre ces trois affections ont-elles été mises en place tant d'années après la découverte des germes pathogènes ? Et pourquoi ces maladies persistent-elles de nos jours ?
En analysant les logiques des politiques sanitaires mises en œuvres, cet ouvrage souligne qu'elles ont été établies en fonction des priorités de l'administration qui sont des priorités économiques. Ainsi se profile l'opposition entre les détenteurs du pouvoir et du savoir, en particulier entre le personnel de la haute administration et les médecins et les infirmiers de terrain.

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