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CEREBROSPINAL FLUID CONTRIBUTION IN THE DIAGNOSIS OF IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME ASSOCIATED WITH CRYPTOCOCCAL MENINGITIS

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ABSTRACT

Objective: Identify cases of Immune Reconstitution Inflammatory Syndrome (IRIS) associated with cryptococcal meningitiswich is defined as a clinical deterioration attributed to the recovery of the immune system during the use of antiretroviral drugs (ART) in patients infected with Human Immunodeficiency Virus (HIV)and show the inflammatory reaction that occurs in the cerebrospinal fluid (CSF). **Methods:** A retrospective study based on medical records of 266 HIV seropositive patients treated at Hospital de Base, São José do Rio Preto, in the period from January 1996 to December 2012 with a diagnosis of cryptococcal meningitis. The criteria of the "International Network for the study of HIV -associated IRIS" (INSHI) for case definitions were used. **Results and Discussion:** 124 patients received ART medication. 27(21.8 %) cases of IRIS were identified. Of the 27 patients with IRIS, 23 (85.2 %) were classified as IRIS-D and4 (14.8 %).The cytological and biochemical analysis of the CF collaborates for the diagnostic screening of IRIS associated with CM, with subsequent association with the criteria of the INSHI. **Conclusions:** Most patients with SIRI showed an inflammatory reaction and increase of leukocytes in the CSF. The inflammatory reaction occurs in the CSF, especially with increased leukocyte and protein. IRIS remains a presumptive diagnosis.

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INTRODUCTION

Cryptococcal Meningitis (CM) is an extremely severe systemic mycosis, with high morbidity and mortality, observed in the advanced stages of the Acquired Immune Deficiency Syndrome (AIDS) (BICANIC & HARRISON, 2004; MENEZES *et al.*, 2014; MARTINS *et al.*, 2015; BALASKO & KEYNAN, 2018; SPEC & POWDERLY, 2018). Acquired Immune Deficiency Syndrome (AIDS) had a radical change in the evolution of patients with this disease with the advent of Highly Active Antiretroviral Therapy (HAART), significantly reducing the mortality and morbidity of AIDS (COLOMBO *et al.*, 2011).

Immune Reconstitution Inflammatory Syndrome (IRIS) is a condition observed in some patients with AIDS, mainly in those with very low T-CD_4 lymphocytes and with high viral load, who at the onset of HAART present a rapid immunological gain when an exaggerated inflammatory response against various infectious agents (viruses, bacteria, fungi) and other situations (neoplasms, autoimmune processes, etc.) (FRENCH *et al.*, 1992; SHELBURNE *et al.*, 2002; SKIEST *et al.*, 2005; BEATTY, 2010; MULLER *et al.*, 2010; JOHNSON & NATH, 2010; COLOMBO *et al.*, 2011; AKILIMALI *et al.*, 2017ELLIS *et al.*, 2018). This syndrome (IRIS) can manifest itself in two ways. The first is to "unmask" a concealed opportunistic infection and the second is to

Table 1. Blood and Cerebrospinal Fluid (CF) laboratory profiles characteristic of patients with Cryptococcal Meningitis at events (IRIS-D, IRIS-P and non-IRIS)

	IRIS-D	IRIS-P	NON-IRIS	P (<0,05)
	n=23	n=4	n=97	
Age (years)	36,1 (20-71)	42,5 (36-50)	35,7 (18-61)	0.2307
Gender	M 20 (87%)	M 4 (100%)	M 71 (73,2%)	
	F 3 (13,0%)		F 26 (26,8%)	
CF Leukocytes (céls/mm^3)	107,0 (5-300)	134,0 (22-295)	43,9 (1-490)	< 0,001
Protein (mg/dl)	102,6 (31-231)	97,3 (48-168)	78,9 (19-410)	0,0127
Glucose (mg/dl)	39,7 (16-63)	35,5 (23-52)	43,1 (2-96)	0.6200
TCD_4 begging of TARV (blood) (céls/mm^3)	68,3 (1-238)	34,5 (17-62)	63 (1-337)	0.8217
	n=22	n=4	n=91	
TCD_4 event (blood) (céls/mm^3)	130,4 (30-489)	168 (103-217)	46,6 (1-421)	< 0,0001
	n=21	n=4	n=87	
Times (Days TARV/Event)	88,8 (8-473)	81,5 (18-237)	710 (1-3753)	< 0,0001

promote a "Paradoxical Reaction" of a previous infection, despite the success of the treatment to which it has been or is undergoing (SUNGKANUPARPH *et al.*, 2009; BEISHUIZEN; 2009; MULLER *et al.*, 2010; JOHNSON & NATH, 2010;HADDOW *et al.*, 2010; LAWN & MEINTJES, 2011; HUIS IN'T VELD *et al.*, 2012; MARTIN-BLONDEL *et al.*, 2012; ARMSTRONG, 2013; ELLIS *et al.*, 2018). In the group of opportunistic infections, Cryptococcal Meningitis (CM) is one of the most important conditions for the AIDS patient, and one of the most frequently found as a result of IRIS. About 400,000 deaths/year in the world are reported in AIDS patients due to CM (VIDAL *et al.*, 2012; MARTINS *et al.*, 2015; COX & PERFECT, 2017). In Latin America, this figure is around 54,000 deaths (MAZUCLOS & GARCIA, 2010).In Brazil, due to the ease of access to Highly Active Antiretroviral Therapy (HAART), CM has been decreasing, but it is still the main cause of meningitis and the second ethology among opportunistic infections affecting the Central Nervous System (CNS) (MAZUCLOS & GARCIA, 2010; COX & PERFECT, 2019). Recent studies performed in Brazil and Argentina show a mortality rate due to MC that ranges from 31.5% to 62.5% (VIDAL *et al.*, 2012).This study identified in patients with AIDS cases of IRIS in MC attended at a hospital service, investigating the correlation of risk factors and laboratory standard of Cerebrospinal Fluid (CF).

MATERIALS AND METHODS

Study participants: A retrospective study was carried out in which the records of 266 HIV-positive human immunodeficiency virus patients attended at a school hospital in Northwest Paulista, from January 1996 to December 2012, diagnosed with MC, were reviewed. The present study was previously approved by the Ethics Committee on Research in Human Beings of the Faculty of Medicine of São José do Rio Preto (FAMERP) according to the opinion number 158/2009. The data obtained (demographics, concomitant infections, use of HAART, T-CD4 lymphocyte dosages) were listed in chronological order, based on the criteria defined by the international network for the study of HIV associated IRIS (INSHI) (HADDOW *et al.*, 2010) for the classification of patients into 3 distinct groups: patients with unmasked IRIS (IRIS-D); patients with paradoxical IRIS (IRIS-P) and non-IRIS patients. We considered as inclusion criteria for unmasked IRIS (IRIS-D): using HAART; CM not recognized at the beginning of HAART; clinical deterioration caused by CM; meningitis with high leukocyte count and an event occurs early after the initiation of HAART. Differently, the inclusion criteria for paradoxical IRIS (IRIS-P) were: using HAART; CM diagnosed pre-HAART by positive culture or typical clinical factors, positive Chinese ink or cryptococcal antigen detection; initial clinical response to antifungal therapy with partial or complete resolution of signs or symptoms, fever or other lesions; event occurs within 12 months of the initiation of HAART and clinical deterioration with meningitis as an inflammatory manifestation. The inclusion criteria for the non-IRIS group were: HAART, and; absence of inflammatory reaction in CF, or; antifungal failure, or; bankruptcy or non-adherence to HAART, or; lack of data, or; another associated opportunistic infection. Exclusion criteria were non-use of HAART.

Laboratory data

The laboratory parameters of CF samples included protein levels, glucose, global leukocyte counts, the presence of cryptococci by Chinese ink microscopy and latex (Cryptococcus Antigen latex agglutination test-Immy®) for cryptococci.

Statistical analysis

The data collected were analysed using the program Graph Pad Instat 3.0 and Prisma 6.01. Descriptive statistical analysis was performed for all variables, based on absolute frequency, percentages, central tendency and dispersion measurements, including interquartile range (IQR). For the statistical analysis of the quantitative variables, the following non-parametric tests were used: Mann-Whitney U test; Wilcoxon's test; Kruskal-Wallis test, with Dunn's Multiple Comparison Test for significant P-values. For the frequency comparisons involving the nominal qualitative variables, the Chi-square test was used. For the establishment of the cut-off point capable of discriminating IRIS and non-IRIS patients and the Odds ratio calculation, ROC curves were constructed. Only curves with an area greater than 0.7000 (70%) were considered adequate for this purpose. The multiple logistic regression method (with stepwise selection method) was also applied, including only the variables that presented a significant value (P-value ≤ 0.05) from the Mann-Whitney test comparison of IRIS and non-IRIS groups. In all analyses, a P-value ≤ 0.05 was considered statistically significant.

RESULTS

Of the 266 CM patients, 124 (46.6%) used HAART and therefore were included in the study. Of these, 27 (21.8%) met the IRIS criteria and 97 (78.2%), non-IRIS. Of the 27 patients

defined as IRIS, 23 (85.2%) were classified as IRIS-D and 4 (14.8%) were IRIS-P. The mean age and gender of the investigated patients were 36 and 20 for IRIS-D, respectively, and 42 years for IRIS-P, all of them male. Among the 97 patients in the non-IRIS group, the mean age was 35.7 years (range 18-61) and 71 (73.2%) were males. The death occurred in 12, 2 and 72 patients, belonging to the IRIS-D, IRIS-P and Non-IRIS groups, respectively. The time between the IRIS event (D and P) and death, with the exception of one case, varied widely, that is, from 8 days to 6 years. The biochemical and cytological patterns of CF for all events, IRIS-D, IRIS-P and non-IRIS are presented in Table 1, considering the number of days between the initiation of HAART and the event. Table 1 demonstrates the epidemiological data, biochemical and cytological parameters of CF and also the time between the beginning of HAART and the IRIS event. In this sense, the values of leukocytes, proteins, T-CD4 and time (days of the HAART/event) showed results with statistical significance between the studied groups. The IRIS-P group had the highest values (134 cells/mm^3) and the non-IRIS, the lowest (43.9cells/mm^3), differing from the IRIS-D group with 107 cells/mm^3. Considering the dosage of proteins, there was an inversion to that described previously, that is, the IRIS-D group had the highest dosages (102.6 mg/dl) and the non-IRIS group, the lowest (78,9mg/dl). Considering the cytological analysis of the blood for T-CD4 determination, at the two moments, beginning of the HAART and the event, the number of cells increased for the IRIS-D and IRIS-P groups and decreased for non-IRIS. It is emphasised in a temporal analysis that the average for the occurrence of IRIS was 85.1 days.

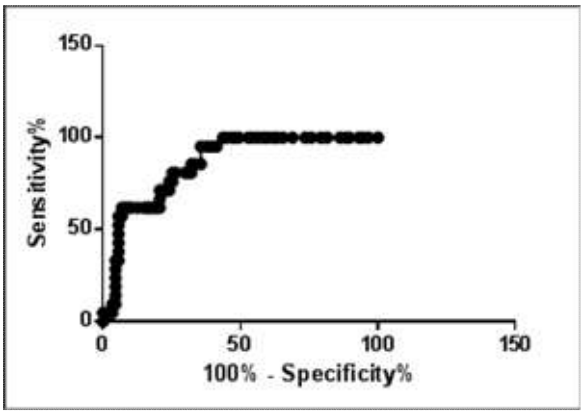

Figure 1. ROC curve for TCD4 analysis in the event

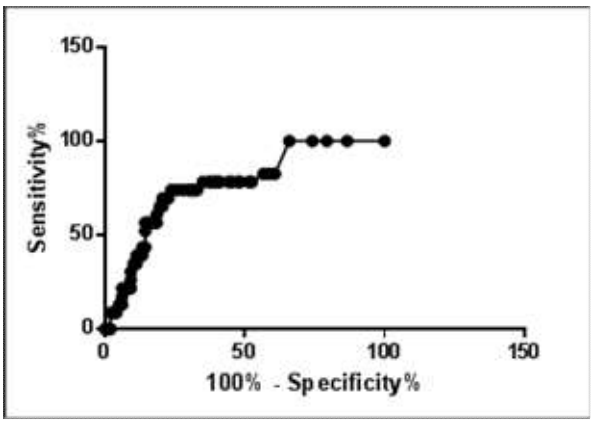

Figure 2. ROC curve for leukocyte analysis

All parameters were reinterpreted by multiple logistic regression analysis between the IRIS and non-IRIS groups. Odds ratio calculations showed that the chance of developing IRIS is 144.5 times greater for patients with a CD4+T cell rate of 40.5 cells/mm^3 (Figure 1, curve area 0.8577) and 49.6 times greater for patients with a leukocyte rate greater than 41.5/mm^3 (Figure 2, curve area 0.7647) after HAART.

DISCUSSION

Since the advent of Highly Active Antiretroviral Therapy (HAART), occurrences of opportunistic infections have been reported with atypical clinical-laboratory presentations (CINTI *et al.*, 2001). In fact, in the current study, the immunological and cytological response patterns in 27 patients (21.8%) with neurocryptococcosis and AIDS illustrate what is described. The data of this research corroborate with the findings of the literature regarding the percentages of occurrence of CM and IRIS, that is, from 2 to 50% (JENNY-AVITAL & ABADI, 2002; LAWN *et al.*, 2005; SHELBURNE *et al.*, 2005; JENKIN & KARSTAEDT, ?; SUNGKANUPARPH *et al.*, 2007; BICANIC *et al.*, 2009; NEYA *et al.*, 2017).The frequency of IRIS-P is higher in published articles, ranging from 8% to 49%, with the inclusion of data from the current research (14.8% -IRIS-P) (LAWN *et al.*, 2005; SHELBURNE *et al.*, 2005; LORTHOLARY *et al.*, 2005; Sungkanuparph *et al.*, 2007; KANBUGU *et al.*, 2008; ANTINORI, *et al.*, 2009; SUNGKANUPARPH *et al.*, 2009; YAN *et al.*, 2015; MEYA *et al.*, 2015; BALASKO & KEYNAN, 2018). Additionally, discordant to the literature, the occurrence of IRIS-D in this study was higher (SHELBURNE *et al.*, 2005; LAWN *et al.*, 2005; BOULWARE *et al.*, 2010; BALASKO & KEYNAN, 2018). All patients in this group showed a proven immune recovery by T-CD4 dosages and did not present neurological signs prior to the diagnosis of IRIS-D. The case classification, based on the INSHI (HADDOW *et al.*, 2010), was established based on the proven immune recovery and absence of neurological signs prior to the diagnosis of IRIS.

Regarding the age and gender of the patients (IRIS-D and IRIS-P), the presented data did not differ with the literature, always with predominance to the male gender (LORTHOLARY *et al.*, 2005; ROBERTSON et al., 2006; BOULWARE *et al.*, 2010; BALASKO & KEYNAN, 2018).The occurrence of death attributed to IRIS, independently of P or D, is low, according to literature data (LAWN *et al.*, 2005; SHELBURNE *et al.*, 2005; BICANIC *et al.*, 2009) with an average of 0 to 15%. In the current study, only one case of death was attributed to IRIS, a patient belonging to group D, and no case to group P. The study by Hadow *et al.* (2010),values different percentages of death occurred in IRIS patients according to (27 to 83%) and in North America, Europe and Asia (0 to 20%), which is why there is no consensus (HADOW *et al.*, 2010). In general, in a review of the literature, CF laboratory parameters (cytology and biochemistry) are commonly valued in the cases of IRIS-P, since this pattern is the most frequent. For IRIS-P, all patients presented an inflammatory reaction, as expected. These patients, after antifungal treatment, presented clinical and laboratory "paradoxical" worsening. The values found in the literature for leukocytes, proteins and glucose in CF vary from 1 to 500 cells/mm^3, from 30 to 152 mg/dl and from 23 to 56 mg/dl, respectively (CINTI *et al.*, 2001; BOELAERT *et al.*, 2004; LORTHOLARY *et al.*, 2005; BROOM *et al.*, 2006; BICANIC *et al.*, 2009; BOULWARE *et al.*, 2010). Although the values of leukocytes and proteins in CF in our study were somewhat lower than those described in the literature, the

majority of IRIS-P patients had a considerable increase in these parameters. In addition, glucose concentrations in CF were equated with published (CINTI *et al.*, 2001; JENNY-AVITAL & ABADI, 2002; BICANIC *et al.*, 2009; BOULWARE *et al.*, 2010). In IRIS-D, in 78% of cases, cellularity and protein concentration parameters were higher compared to the literature (WOODS et al., 1998; SHELBURNE *et al.*, 2005; SUNGKANUPARPH *et al.*, 2009; BICANIC *et al.*, 2009; BOULWARE *et al.*, 2010), probably due to the strict criteria used. We reiterate here the statements by Broom *et al.* (2006) on the immune reconstitution in meningitis, where clinical signs and symptoms are amplified due to the intense inflammatory response. Similarly, corroborating with a study by Lortholary *et al.* (2005), cases of IRIS-P also showed higher leukocyte and protein values. The analysis of cellularity and protein results for the 3 groups in the current study showed statistically significant differences, proving that the inflammatory reaction, in fact, occurs in patients with IRIS. Additionally, glucose parameters did not differ between groups, corroborating with data from the literature (CINTI *et al.*, 2001; BICANIC *et al.*, 2009; BOULWARE *et al.*, 2010). In the differential cytological analysis, neutrophilic predominance, especially for the IRIS-D group, justified the significant statistical difference found. This result is understood and expected, according to the study by Zhang *et al.* (2016) which states that neutrophil chemotaxis occurs during infection by Cryptococcus neoformans mediated primarily by complement factor C3 and expression of the cell marker CD11B. Certainly, these results would be expected for the cases of IRIS-P, however, mediating the small casuistry were not judged.

It is interesting to note here a greater recovery of the immune response, established by the TCD4 cell count when compared to the literature for IRIS cases (WOODS et al., 1998; CINTI *et al.*, 2001; LAWN *et al.*, 2005; SHELBURNE *et al.*, 2005; LORTHOLARY *et al.*2005; BICANIC *et al.*, 2006; SUNGKANUPARPH *et al.*, 2007; BICANIC *et al.*, 2009; KANBUGU *et al.*, 2008; ANTINORI, *et al.*, 2009; BALASKO & KEYNAN, 2018). This parameter, with a statistically significant difference between IRIS and NO IRIS groups, can be used as a marker. The IRIS-D in the present investigation occurred in an average of 89 days (var. 8 to 473) from the start of HAART. The highest and the lowest time found for the development of IRIS-D in the current literature after the initiation of HAART was described by Lortholary *et al.* (2005) for 240 days and Manabe *et al.* (2007) for 4 days, respectively. Therefore, there is no consensus for this parameter, a fact previously observed by Antinori (2013). Again, there was an agreement in the temporal analysis between the initiation of HAART in the IRIS-P group (82 days). In this sense, the largest and smallest period of time found in the literature was presented by the study of Shelburne *et al.* (2005) (330 days) and Lawn *et al.* (2005) (7 days). The diagnosis of IRIS is presumptive as there is no specific marker. In this sense, the cytological and biochemical analysis of the CF collaborates for the diagnostic screening of IRIS associated with CM, with subsequent association with the criteria of the INSHI.

REFERENCES

Akilimali, N. A., Chang, C. C., Muema, D. M., Reddy, T., Moosa, M. S., Lewin, S. R., French, M. A., and Ndung'u, T. 2017. Plasma but not cerebrospinal fluid interleukin 7 and interleukin 5 levels pre-antiretroviral therapy commencement predict cryptococcosis-associated immune reconstitution inflammatory syndrome. Clin Infect Dis. 65, pp. 1551-1559. https://doi.org/10.1093/cid/cix598

Antinori, S. (2013) New insights into HIV/AIDS-associated cryptococcosis. ISRN Aids. 2013, 471363. https://doi.org/10.1155/2013/471363

Antinori, S., Ridolfo, A., Fasan, M., Magni, C., Galimberti, L., Milazzo, L., Sollima, S., Adorni, F., Giuliani, G., Galli, M., Corbellino, M., and Parravicini, C. (2009) AIDS-associated cryptococcosis: a comparison of epidemiology, clinical features and outcome in the pre- and post-HAART eras. Experience of a single centre in Italy. HIV Med. 10, pp. 6-11. https://doi.org/10.1111/j.1468-1293.2008.00645.x

Armstrong, W. S. (2013) The immune reconstitution inflammatory syndrome: a clinical update. Curr Infect Dis Rep. 15, PP. 39-45. https://doi.org/10.1007/s11908-012-0308-y

Balasko, A., and Keynan, Y. (2018) Shedding light on IRIS: from pathophysiology to treatment of cryptococcal meningitis and Immune Reconstitution Inflammatory Syndrome in HIV-infected individuals. HIV Med. 20, pp. 1-10. https://doi.org/10.1111/hiv.12676

Beatty, G. W. (2010). Immune reconstitution inflammatory syndrome. Emerg Med Clin North Am. 28, 393-407. https://doi.org/10.1016/j.emc.2010.01.004

Beishuizen, S. J. E., and Geerlings, S. E. (2009) Immune reconstitution inflammatory syndrome: immunopathogenesis, risk factors, diagnosis, treatment and prevention. J Med. 67, pp. 327-331. http://www.njmonline.nl/getpdf.php?id=854

Bicanic, T., and Harrison, T. S. (2004) Cryptococcal meningitis. Br Med Bull. 72, pp. 99-118. https://doi.org/10.1093/bmb/ldh043

Bicanic, T., Harrison, T., Niepieklo, A., Dyakopu, N., and Meintjes, G. (2006) Symptomatic relapse of HIV-associated cryptococcal meningitis after initial fluconazole monotherapy: the role of fluconazole resistance and immune reconstitution. Clin Infect Dis. 43, pp. 1069-1070. https://doi.org/10.1086/507895

Bicanic, T., Meintjes, G., Rebe, K., Williams, A., Loyse, A., Wood, R., Hayes, M., Jaffar, S., and Harrison, T. (2009) Immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis: a prospective study. J Acquir Immune DeficSyndr. 51, pp. 130-134. https://doi.org/10.1097/QAI.0b013e3181a56f2e.

Boelaert, J. R., Goddeeris, K. H., Vanopdenbosch, L. J., and Casselman, J. W. (2004) Relapsing meningitis caused by persistent cryptococcal antigens and immune reconstitution after the initiation of highly active antiretroviral therapy. AIDS. 18, pp. 1223-1224. https://doi.org/10.1097/00002030-200405210-00023

Boulware, D. R., Bonham, S. C., Meya, D. B., Wiesner, D. L., Park, G. S., Kambugu, A., Janoff, E. N., and Bohjanen, P. R. (2010) Paucity of initial cerebrospinal fluid inflammation in cryptococcal meningitis is associated with subsequent Immune Reconctitution Inflammatory Syndrome. J Infect Dis. 202, pp.962-970. https://doi.org/10.1086/655785

Broom, J., Woods, M., and Allworth, A. 2006. Immune reconstitution inflammatory syndrome producing atypical presentations of cryptococcal meningitis: case report and a review of immune reconstitution-associated cryptococcal

infections. Scand J Infect Dis. 38, pp. 219-221. https://doi.org/10.1080/00365540500333996

Cinti, S. K., Armstrong, W. S., and Kauffman, C. A. 2001. Case report. Recurrence of increased intracranial pressure with antiretroviral therapy in an AIDS patient with cryptococcal meningitis. Mycoses. 44, pp. 497-501. https://doi.org/10.1046/j.1439-0507.2001.00663.x

Colombo, E. R. C., Mora, D. J., and Silva-Vergara, M. L. (2011) Immune reconstitution inflammatory syndrome (IRIS) associated with Cryptococcus neoformans infection in AIDS patients. Mycoses. 54, e178-e182. https://doi.org/10.1111/j.1439-0507.2010.01870.x

Cox, G. M., and Perfect, J. R. (2018) Epidemiology, clinical manifestations, and diagnosis of cryptococcal meningoencephalitis in HIV-infected patients. https://www.uptodate.com/contents/epidemiology-clinical-manifestations-and-diagnosis-of-cryptococcus-neoformans-meningoencephalitis-in-hiv-infected-patients

Cox, G. M., and Perfect, J. R. (2019) Microbiology and epidemiology of Cryptococcus neoformans infection. https://www.uptodate.com/contents/microbiology-and-epidemiology-of-cryptococcus-neoformans-infection

Ellis, J. P., Kalata, N., Joekes, E. C., Kampondeni, S., Benjamin, L. A., Harrison, T. S., Lalloo, D. G., and Heyderman, R. S. (2018) Ischemic stroke as a complication of cryptococcal meningitis and immune reconstitution inflammatory syndrome: a case report. BMC Infect Dis. 18, pp. 520. https://doi.org/10.1186/s12879-018-3386-0

French, M. A., Mallal, S. A., and Dawkins, R. L. (1992) Zidovudine-induced restoration of cell-mediated immunity to mycobacteria in immunodeficient HIV-infected patients. AIDS. 6, pp. 1293-1297. https://doi.org/10.1097/00002030-199211000-00009

Haddow, L. J., Colebunders, R., Meintjes, G., Lawn, S. D., Elliott, J. H., Manabe, Y. C., Bohjanen, P. R., Sungkanuparph, S., Easterbrook, P. J., French, M. A., Boulware, D. R., and International Network for the Study of HIV-associated IRIS (INSHI). (2010) Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. Lancet Infect Dis. 10, pp. 791-802. https://doi.org/10.1016/S1473-3099(10)70170-5

Haddow, L. J., Colebunders, R., Meintjes, G., Lawn, S. D., Elliott, J. H., Manabe, Y. C., Bohjanen, P. R., Sungkanuparph, S., Easterbrook, P. J., French, M. A., Boulware, D. R., and International Network for the Study of HIV-associated IRIS (INSHI). (2010) Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. Lancet Infec Dis. 10, pp. 791-802. https://doi.org/10.1016/S1473-3099(10)70170-5

Huisin´t Veld, D., Sun, H. Y., Hung, C. C., and Colebunders, R. (2012) The immune reconstitution inflammatory syndrome related to HIV co-infections: a review. Eur J ClinMicrobiol Infect Dis. 31, pp. 919-927. https://doi.org/10.1007/s10096-011-1413-9

Jenkin, L., and Karstaedt, A. (2019) Cryptococcal complications in the first year on HAART: experiences of a South African antiretroviral programme. XVI International Aids Conference; Toronto, 13-18 August, p. Abstract THPE0080. https://i-base.info/htb/keyword/conference-index

Jenny-Avital, E. R., and Abadi, M. (2002) Immune reconstitution cryptococcosis after initiation of successful highly active antiretroviral therapy. Clin Infect Dis. 35, pp. e128-e133. https://doi.org/10.1086/344467

Johnson, T., and Nath, A. (2010) Neurological complications of immune reconstitution in HIV-infected populations. Ann N Y Acad Sci. 1184, 106-120. https://doi.org/10.1111/j.1749-6632.2009.05111.x

Kambugu, A., Meya, D. B., Rhein, J., O'Brien, M., Janoff, E. N., Ronald, A. R., Kamya, M. R., Mayanja-Kizza, H., Sande, M. A., Bohjanen, P. R., and Boulware, D. R. (2008) Outcomes of cryptococcal meningitis in Uganda before and after the availability of highly active antiretroviral therapy. Clin Infect Dis. 46, pp. 1694-1701. https://doi.org/10.1086/587667

Lawn, S. D., and Meintjes, G. (2011) Pathogenesis and prevention of immune reconstitution disease during antiretroviral therapy. Expert Rev Ant Infect Ther. 9, PP. 415-430. https://doi.org/10.1586/eri.11.21

Lawn, S. D., Bekker, L. G., Myer, L., Orrell, C., and Wood, R. (2005) Cryptococcocal immune reconstitution disease: a major cause of early mortality in a South African antiretroviral programme. AIDS. 19, pp. 2050-2052. https://doi.org/10.1097/01.aids.0000191232.16111.f9

Lortholary, O., Fontanet, A., Mémain, N., Martin, A., Sitbon, K., Dromer, F., and French Cryptococcosis Study Group. (2005) Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France. AIDS. 19, pp. 1043-1049. https://doi.org/10.1097/01.aids.0000174450.70874.30

Manabe, Y. C., Campbell, J. D., Sydnor, E., and Moore, R. D. (2007) Immune reconstitution inflammatory syndrome: risk factors and treatment implications. J Acquir Immune Defic Syndr. 46, pp. 456-462. https://doi.org/10.1097/qai.0b013e3181594c8c

Martin-Blondel, G., Mars, L. T., and Liblau, R. S. (2012) Pathogenesis of the immune reconstitution inflammatory syndrome in HIV-infected patients. CurrOpin Infect Dis. 25, pp. 312-320. https://doi.org/10.1097/QCO.0b013e328352b664

Martins, M. A., Brighente, K. B. S., Matos, T. A., Vidal, J. E., Hipólito, D. D. C., and Pereira-Chioccola, V. L. (2015) Molecular diagnosis of cryptococcal meningitis in cerebrospinal fluid: comparison of primer sets for Cryptococcus neoformansand Cryptococcus gattii species complex. Braz J Infect Dis. 19, pp. 62-67. https://doi.org/10.1016/j.bjid.2014.09.004

Mazuelos, E. M., and Garcia, A. I. A. (2010) Aspectos microbiológicos de lacriptococosis em la era post-TARGA. EnfermInfeccMicrobiolClin. 28, pp. 40-45. https://doi.org/10.1016/S0213-005X(10)70007-0

Menezes, T., Scain, G., Quadros, R. M., Miletti, L. C., Souza, A. L., Miguel, R. L., and Marques, S. M. T. (2014). Cryptococcus spp. em excretas de pombos (Columbalivia) de áreas públicas de Lages, Santa Catarina. SciAnim Health. 2, pp. 102-114. https://doi.org/10.15210/sah.v2i2.4109

Meya, D. B., Okurut, S., Zziwa, G., Cose, S., Bohjanen, P. R., Mayanja-Kizza, H., Joloba, M., Boulware, D. R., Yukari Manabe, C., Wahl, S., and Janoff, E. N. (2017) Monocyte Phenotype and IFN-gamma-Inducible Cytokine Responses Are Associated with Cryptococcal Immune Reconstitution Inflammatory Syndrome. J Fungi (Basel). 3, pp. 28. https://doi.org/10.3390/jof3020028

Meya, D. B., Okurut, S., Zziwa, G., Rolfes, M. A., Kelsey, M., Cose, S., Joloba, M., Naluyima, P., Palmer, B. E., Kambugu, A., Mayanja-Kizza, H., Bohjanen, P. R., Eller, M. A., Wahl, S. M., Boulware, D. R., Manabe, Y. C., and Janoff, E. N. (2015) *Cellular immune activation in cerebrospinal fluid from Ugandans with cryptococcal meningitis and immune reconstitution inflammatory syndrome*. J Infect Dis. 211, pp. 1597-1606. https://doi.org/10.1093/infdis/jiu664

Müller, M., Wandel, S., Colebunders, R., Attia, S., Furrer, H., and Egger, M. (2010) Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV-infection: a systematic review and meta-analysis. Lancet Infect Dis. 10, 251-261. https://doi.org/10.1016/S1473-3099(10)70026-8

Robertson, J., Meier, M., Wall, J., Ying, J., and Fichtenbaum, C. J. (2006) Immune reconstitution syndrome in HIV: validating a case definition and identifying clinical predictors in persons initiating antiretroviral therapy. Clin Infect Dis. 42, pp. 1639-1646. https://doi.org/10.1086/503903

Shelburne, S. A. 3rd., Darcourt, J., White, A. C. Jr., Greenberg, S. B., Hamill, R. J., Atmar, R. L., and Visnegarwala, F. (2005) The role of immune reconstitution inflammatory syndrome in AIDS-related Cryptococcus neoformans disease in the era of highly active antiretroviral therapy. Clin Infect Dis. 40, pp. 1049-1052. https://doi.org/10.1086/428618

Shelburne, S. A. 3rd., Hamill, R. J., Rodriguez-Barradas, M.C., Greenberg, S. B., Atmar, R. L., Musher, D. W., Gathe, J. C. Jr., Visnegarwala, F., and Trautner B. W. (2002) Immune reconstitution inflammatory syndrome: Emergence of a unique syndrome during highly active antiretroviral therapy. Medicine. 81, pp. 213-227. https://doi.org/10.1097/00005792-200205000-00005

Shelburne, S. A., Visnegarwala, F., Darcourt, J., Graviss, E. A., Giordano, T. P., White, A. C. Jr., and Hamill, R. J. (2005) Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. AIDS. 19, pp. 399-406. https://doi.org/10.1097/01.aids.0000161769.06158.8a

Skiest, D. J., Hester, L. J., and Hardy, R. D. (2005) Cryptococcal immune reconstitution inflammatory syndrome: report of four cases in three patients and review of the literature. J Infect. 51, 289-297. https://doi.org/10.1016/j.jinf.2005.02.031

Spec, A., and Powderly, W. G. (2018) Cryptococcal meningitis in AIDS. HandbClin Neurol. 152, pp. 139-150. https://doi.org/10.1016/B978-0-444-63849-6.00011-6

Sungkanuparph, S., Filler, S. G., Chetchotisakd, P., Pappas, P. G., Nolen, T. L., Manosuthi, W., Anekthananon, T., Morris, M. I., Supparatpinyo, K., Kopetskie, H., Kendrick, A. S., Johnson, P. C., Sobel, J. D., and Larsen, R. A. (2009) Cryptococcal immune reconstitution inflammatory syndrome after antiretroviral therapy in AIDS patients with cryptococcal meningitis: a prospective multicenter study. ClinInfec Dis. 49, 931-934. https://doi.org/1010.1086/605497

Sungkanuparph, S., Jongwutiwes, U., and Kiertiburanakul, S. (2007) Timing of cryptococcal immune reconstitution inflammatory syndrome after antiretroviral therapy in patients with AIDS and cryptococcal meningitis. J Acquir Immune DeficSyndr. 45, pp. 595-596. https://doi.org/10.1097/QAI.0b013e318061b5eb

Vidal, J. E., Gerhardt, J., Peixoto de Miranda, E. J., Dauar, R. F., Oliveira Filho, G. S., Penalva de Oliveira, A. C., and Boulware, D. R. (2012) Role of quantitative CSF microscopy to predict culture status and outcome in HIV-associated cryptococcal meningitis in a Brazilian cohort. DiagnMicrobiol Infect Dis. 73, pp. 68-73. https://doi.org/10.1016/j.diagmicrobio.2012.01.014

Woods, M. L., MacGinley, R., Eisen, D. P., and Allworth, A. M. (1998) HIV combination therapy: partial immune restitution unmasking latent cryptococcal infection. AIDS. 12, pp. 1491-1494. https://doi.org/10.1097/00002030-199812000-00011

Yan, S., Chen, L., Wu, W., Li, Z., Fu, Z., Zhang, H., Xue, J., Hu,Y., Mou, J., and Fu, C. (2015) Paradoxical immune reconstitution inflammatory syndrome associated with cryptococcal meningitis in China: a 5-year retrospective cohort study. ClinMicrobiol Infect. 21, pp. 379.e11-4. https://doi.org/10.1016/j.cmi.2014.11.011

Zhang, M., Sun, D., Liu, G., Wu, H., Zhou, H., and Shi, M. (2016) Real-time in vivo imaging reveals the ability of neutrophils to remove Cryptococcus neoformans directly from the brain vasculature. J Leukoc Biol. 99, pp. 467-473. https://doi.org/10.1189/jlb.4AB0715-281R

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