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CD8 + T-lymphocyte Encephalitis: A Systematic Review

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Abstract

The increase of CD8 + T lymphocytes in the perivascular spaces of patients with HIV encephalopathy has been reported in some studies. CD8 + T lymphocyte encephalitis was first described in 2013 and then a few other similar cases were published. We proposed to analyze the clinical, MR imaging, and histopathology findings of CD8 + T lymphocyte encephalitis. A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyzes protocol using the PubMed, Scopus, Lilacs, and IBECS databases up to February 3, 2018. Seven articles were included, two case series and five case reports. A total of 19 individuals were evaluated. MRI showed alterations in the white matter signal in all cases. Histopathology showed a predominance of CD8 + T lymphocytes. The findings described so far may resemble the inflammatory immune reconstitution syndrome. New studies on the subject are needed in an attempt to characterize the differences between these two entities. **(AIDS Rev. (ahead of print))**

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Key words

HIV. CD8 + T lymphocytes. Encephalitis. Magnetic resonance imaging.

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Introduction

In the context of HIV, the CD8 + T lymphocyte assists in controlling viral replication, exerting a cytotoxic effect on CD4 + T lymphocytes infected by HIV. Some patients have CD8 + lymphocytosis, and this finding has been related to some diseases due to the infiltration of some organs by it[1].

Since 2003, some studies have shown a lymphocyte increase CD8 + in the perivascular spaces in the brain of patients with encephalopathy related to HIV (HIVE)[2-4].

Although previous studies suggest the disease, CD8 + T lymphocyte encephalitis was named and described for the first time in 2013 by Lescure et al.[5] which observed a pattern of perivascular linear enhancement in MRI contrast medium and extensive CD8 + T lymphocyte infiltrate with perivascular predominance in the anatomopathological study. After this study, some other similar cases were published some treated with corticotherapy as proposed by Lescure et al. 2013[5] and others treated with another form of immunosuppression[6] or only with the change in combined antiretroviral therapy (cART)[7].

Since it is a newly described entity with still uncertain patterns and pathophysiology, this systematic review aims to summarize, evaluate, and analyze all the cases described in the literature as encephalitis by CD8 + T lymphocytes. To the best of our knowledge, this is the first systematic review on the topic.

Methods

This systematic review was conducted according to the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-analyzes[8]. The protocol was registered in Prospero's database (International Prospective Register of Systematic Reviews) by the number CRD42018090258.

We included articles of encephalitis by CD8 + T lymphocytes in humans infected by HIV. We excluded review articles, articles dealing with encephalitis by other etiologies and animal studies.

The following databases were used: PubMed, Lilacs, IBECS, and Scopus. In a complementary way, a manual analysis of references of articles included in the review was performed, as well as analysis of citations through Google Scholar.

The search of articles in the databases was performed on February 3, 2018, and was used as Mesh

Table 1. PubMed's search strategy

Search	Add to builder	Query	Items found	Time
#11	Add	Search ((#10) AND #8) AND #9	17	08:37:25
#10	Add	Search "CD8-Positive T-Lymphocytes"[Mesh] OR "CD8 Positive T Lymphocytes"[All Terms] OR "CDB- Positive T-Lymphocyte"[All Terms] OR "T.Lymphocyte, CD8.Positive"[All Terms] OR "T.Lymphocytes, CD8-Positive"[All Terms] OR "T8 Lymphocytes"[All Terms] OR "Lymphocyte, T8"[All Terms] OR "Lymphocytes, T8"[All Terms] OR "T8 Lymphocyte"[All Terms] OR "T8 Cells"[All Terms] OR "Cell, T8" [All Terms] OR "Cells, T8"[All Terms] OR "T8 Cell"[All Terms] OR "CD8.Positive Lymphocytes"[All Terms] OR "CD8 Positive Lymphocytes"[All Terms] OR "CD8-Positive Lymphocyte"[All Terms] OR "Lymphocyte, CD8-Positive"[All Terms] OR "Lymphocytes, CD8.Positive"[All Terms]	57689	08:36:09
#9	Add	Search "HIV"[Mesh] OR "Human Immunodeficiency Virus"[All Terms] OR "Immunodeficiency Virus, Human"[All Terms] OR "Immunodeficiency Viruses, Human"[All Terms] OR "Virus, Human Immunodeficiency"[All Terms] OR "Viruses, Human Immunodeficiency"[AIII Terms] OR "Human Immunodeficiency Viruses"[All Terms] OR "AIDS Virus"[All Terms] OR "AIDS Viruses"[All Terms] OR "Virus, AIDS"[All Terms] OR "Viruses, AIDS"[All Terms] OR "Acquired Immune Deficiency Syndrome Virus"[All Terms] OR "Acquired Immunodeficiency Syndrome Virus"[All Terms]	143691	08:35:28
#8	Add	Search ""Encephalitis"[Mesh] OR "Brain Inflammation"[All Terms] OR "Inflammation, Brain"[All Terms] OR "Brain Inflammations"[All Terms]	45491	08:33:02
#7	Add	Search ((CD8+) AND encephalitis) AND HIV	104	08:32:44

terms HIV, CD8-Positive T-lymphocytes, and encephalitis with their respective Entry terms. PubMed's search strategy is available in table 1. No date or language limit was used during the search.

The analysis of the title and summary of articles found were performed by two independent reviewers (LMS and EAV) and the abstracts that did not provide enough data were maintained for the full-text analysis. Independent reviewers performed the full-text analysis and judged the inclusion and exclusion criteria for articles to be included in the study. Disagreements were resolved by consensus and, when necessary, the opinion of a third reviewer (MRJ) was taken into account.

The quality of the articles was evaluated through specific validated instruments for each type of design included in the study by two independent reviewers (LMS and EAV). For the case series, we used the instrument published by GUO et al. 2016[9], which takes into account the purpose of the study, the study population, the intervention, the evaluation of the results, and the statistical analysis.

For the case reports were used the instrument published by Moola et al., 2015[10], consists of eight questions that analyze the case description, the diagnostic methods used, the intervention, the post-intervention clinic, the adverse effects of the intervention, and the relevance of the case to the literature.

Articles of acceptable quality were considered to be articles that met at least 70% of the evaluation criteria.

Two independent reviewers performed the data extraction (LMS and EAV), and disagreements were analyzed by a third reviewer (MRJ). The following were collected: last name of the first author; year of publication; country of origin; purpose of the study; study design; follow-up time; number of individuals analyzed; age; sex; ethnicity; levels of CD4 +; and CD8 + T lymphocytes; image characteristics; characteristics of the pathology; clinic; treatment; and outcome.

Results

The initial research identified 250 articles being 89 duplicates. After removing the duplicates, 161 articles went to title and abstract analysis. Of these, 26 articles were selected for the full-text analysis and seven met the inclusion criteria.

The analysis of references and citations identified six articles for the full-text analysis; however, none of them fulfilled all the inclusion criteria. Seven articles were included in this systematic review. Figure 1 shows the flowchart of the selection of the articles.

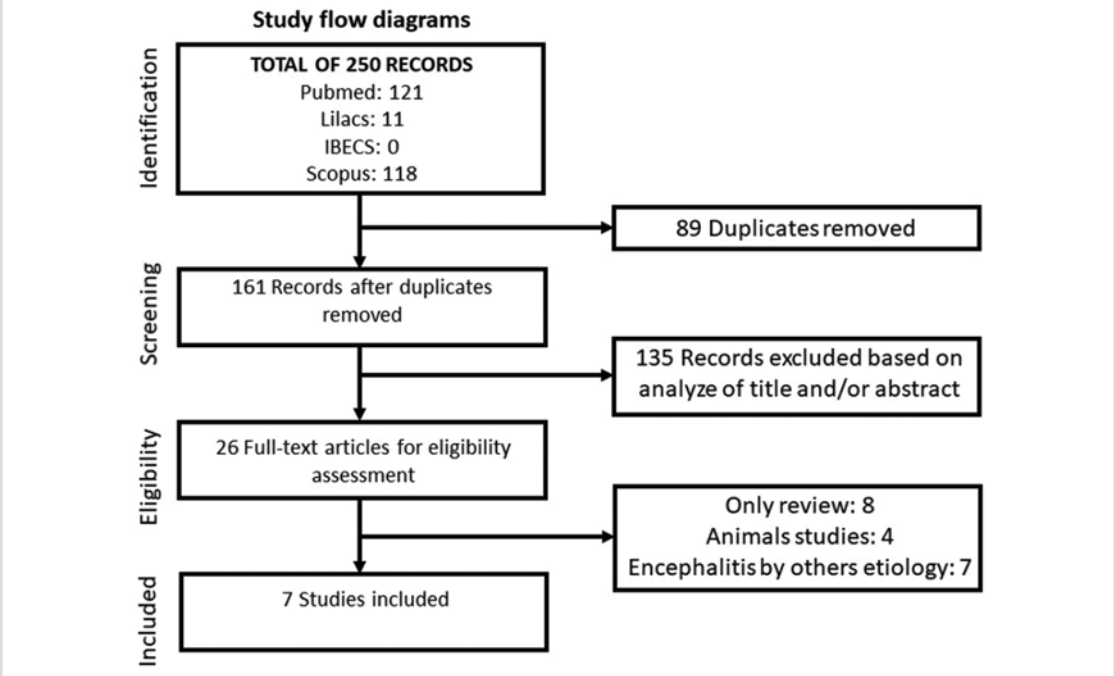

Figure 1. *The flowchart of the selection of the articles.*

Table 2. The characteristics of the included studies

Studies characteristics							
Trial	**Year**	**Country**	**Aim of the study**	**Study design**	**Data collection time range**	**Age**	**Sujects total**
Lescure et al.[5]	2013	France	Describe the clinical, radiological, and pathological features of and outcome of 14 cases of a new form of HIV-related encephalitis	Case series	13 years	25-59	14
Gray et al.[11]	2013	France	Describe the neuropathological findings in 10 biopsy cases and one autopsy case of encephalitis with heavy infiltration of CD8+ lymphocytes in HIV-infected patients receiving cART	Case series	NI	25-54	10
Moulignier et al.[1]	2013	France	Describe the first biopsy-proven focal CD8E mimicking a brain tumor in a HIV+ patient	Case report	2 years	27	1
Moulignier et al.[12]	2014	France	Report the first case of spinal cord involvement by CD8+	Case report	5 years	52	1
Morioka et al.[7]	2016	Japan	Present a case of CD8E that was presumed to have been caused by the inflammatory host immune response to drug-resistant HIV	Case report	NI	52	1
Zarkali et al.[13]	2017	UK	Report a woman with CD8E, with a normal CD4 count and undetectable serum viral load, who made a good recovery	Case report	NI	52	1
Salam et al.[6]	2016	UK	Report a case of CD8+E where the initial positive response to steroid treatment was followed by several relapses on withdrawal	Case report	9 years	34	1

cART, combined antiretroviral therapy; NI, not informed.

The included studies were published between 2013 and 2016, being two case series and five case reports. The number of individuals reported in the case series was 14 and 10, the last being in common with the first study, so 19 individuals were evaluated in this systematic review, nine men and ten women, aged between 27 and 59 years. Patient follow-up ranged from 2 to 13 years between studies. The characteristics of the included studies are presented in table 2.

The case series of Lescure et al., 2013[5], met 77% of the adopted criteria for quality analysis while the case series of Gray et al., 2013[11], fulfilled 72% of the criteria.

Among the case reports, only Salam et al., 2016[6], and Morioka et al., 2016[7], did not meet 100% of the quality criteria but were still considered satisfactory.

Four patients in the case series of Lescure et al., 2013[5], and the case of Salam et al., 2016[6], had a diagnosis presumed by the clinical picture, while the other patients had anatomopathological evidence at brain biopsy.

Table 3a and b summarizes the quality of the studies included analysis.

Lescure et al., 2013[5], were the first to correlate anatomopathological findings with changes in MRI and clinical presentation, denominating such as CD8 + encephalitis disease. They described 14 cases of HIV patients diagnosed with encephalitis of indeterminate etiology that presented linear or punctate multiple contrast enhancement on MRI. The diffusion sequence was performed in only four of the 14 patients and all of them presented restriction in regions that showed contrast enhancement. Eight of the 14 patients were considered to be immunologically stable, ten underwent brain biopsy and four had the presumed diagnosis by the clinical, one case being submitted to autopsy. Biopsies showed microglial activation and reactive astrocytes with infiltration by T lymphocytes with the predominance of CD8 +.

Patients were treated with methylprednisolone, with only 30% of patients recovering completely and the earlier the treatment started, the better the prognosis.

Gray et al., 2013[11], describe in detail the pathology's findings of the ten patients submitted to brain biopsy described in the case series of Lescure et al., 2013[5]. Reactive astrocytes and microglial activation were found in all cases, five of which showed a weak reaction of HIV-p24 protein in macrophages and microglial cells. Diffuse infiltration of T lymphocytes, mostly CD8 +, with a variable amount of CD4 + T lymphocytes, was observed in all cases. In patients who died, it was observed severe inflammation, almost totally composed of CD8 + T lymphocytes, with weak or absent reaction CD4 + and the one of them that had some CD4 + had a low CD4 +/CD8 + ratio. Infiltration by CD8 + T lymphocytes predominated in the perivascular regions. In most cases, it was the infiltration of vessel walls by lymphocytes, suggestive of lymphocytic vasculitis, but one case showed changes similar to multiple sclerosis or acute disseminated encephalomyelitis (ADEM).

Moulignier et al., 2013[1], reported a case of CD8 + focal encephalitis which the MRI presented as multiple enhancement intra-axial lesions in the right cerebral hemisphere with significant perilesional edema and mass effect, similar to swelling lesion. Biopsy showed intense infiltration by CD8 + T lymphocytes and microglial activation, as described by Gray et al., 2013[1]. The patient was treated with corticosteroids presenting clinical improvement, and death 1 year after the first hospitalization.

Moulignier et al., 2014[12], described the first case of CD8 + transverse myelitis in a patient who was also diagnosed with CD8 + encephalitis after brain biopsy. MRI showed numerous intramedullary lesions with T2 hypersignal, some with contrast enhancement and irregular enhancement in the head of the caudate nucleus. The patient was treated according to the scheme proposed by Lescure et al., 2013[5], and presented complete clinical improvement.

Morioka et al., 2016[7], reported the first case of CD8 + encephalitis based on cerebral biopsy and clinical, which was treated with the exchange of the antiretroviral regimen. MRI showed severe cerebral atrophy and diffuse leukoencephalopathy in FLAIR without contrast enhancement.

Zarkali et al., 2017[13], reported a case of CD8 + encephalitis in which MRI showed diffuse and symmetrical hypersignal in T2 of the white matter and deep gray matter with diffusion restriction at the periphery of the white matter confluence. The biopsy showed lymphocytic meningoencephalitis with a predominance of CD8 + T lymphocytes. The patient was treated with corticosteroid therapy and antiretroviral regimen exchange and showed complete clinical improvement.

Salam et al., 2016[6], described the first case of CD8 + encephalitis that associated mycophenolate and corticosteroid therapy. MRI showed changes in the white matter signal without contrast enhancement and expansive effect. The patient presented several episodes of encephalopathy of indeterminate origin responsive to corticosteroid therapy, which during the weaning presented the symptoms again. Therefore, mycophenolate was used as an alternative to reduce the corticosteroid dose.

In all cases, opportunistic CNS infections were excluded from the study.

A total of 19 individuals were evaluated in this systematic review, of which 12 (63.1%) were Afro-descendant. The patient's ages ranged from 27 years to 59 years, and the mean age was 41.8 years. There was a slight predominance in the female gender (52.6%) and the outcome was more favorable in the male gender, where five of the nine evaluated individuals had total recovery and only one died during

Table 3a. The quality of the studies included, (a) case reports studies

Critical appraisal of the case reports studies (The Joanna Briggs Institute)	Moulignier et al.[1]	Moulignier et al.[12]	Morioka et al.[7]	Zarkali et al.[13]	Salam et al.[6]
Were patient's demographic characteristics clearly described?	+	+	+	+	Unclear
Was the patient's history clearly described and presented as a timeline?	+	+	+	+	+
Was the current clinical condition of the patient on presentation clearly described?	+	+	+	+	+
Were diagnostic tests or assessment methods and the results clearly described?	+	+	+	+	+
Was the intervention(s) or treatment procedure(s) clearly described?	+	+	+	+	+
Was the post-intervention clinical condition clearly described?	+	+	+	+	+
Were adverse events (harms) or unanticipated events identified and described?	+	–	Unclear	+	+
Does the case report provide takeaway lessons?	+	+	+	+	+

Table 3b. The quality of the studies included, (b) case series studies

Critical appraisal of the case series studies (modified Delphi technique)	Lescure et al.[5]	Gray et al.[11]
Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction, or methods section?	+	+
Are the characteristics of the participants included in the study described?	+	+
Were the cases collected in more than one center?	+	+
Are the eligibility criteria (inclusion and exclusion criteria) to entry the study explicit and appropriate?	+	+
Were participants recruited consecutively?	–	–
Did participants enter the study at a similar point in the disease?	+	+
Was the intervention clearly described in the study?	+	+
Were additional interventions (cointerventions) clearly reported in the study?	+	+
Are the outcome measures clearly defined in the introduction or methods section?	+	+
Were relevant outcomes appropriately measured with objective and/or subjective methods?	+	+
Were outcomes measured before and after intervention?	+	+
Were the statistical tests used to assess the relevant outcomes appropriate?	+	–
Was the length of follow-up reported?	+	–
Was the loss to follow-up reported?	+	–
Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	+	–
Are adverse events reported?	+	+
Are the conclusions of the study supported by results?	+	+
Are both competing interests and source of support for the study reported?	+	–

the follow-up time. In the female gender, four had total recovery and four died during follow-up. Deaths occurred between 1 and 12 months, with an average of 6.8 months.

Seven individuals had symptoms of minor infections days before the onset of the disease, two had stopped treatment with cART, two were considered viral escape, two had immune reconstitution syndrome (IRIS), one had been identified resistance to antiretroviral treatment, and the other had no possible triggers identified and/or reported.

Among the reported cases, 11 subjects had cerebrospinal fluid (CSF) CD8 + T lymphocyte infiltration during the reported encephalitis. These levels ranged from 47% to 87% of CD8 + subtype T lymphocytes with a mean of 72.8%, and only one patient of these 11 presented values lower than 65%.

Among the changes observed in MRI, 16 individuals presented some contrast enhancement, highlighting the perivascular linear pattern described in the case series, and all of them presented a signal alteration in the white matter in the FLAIR sequence and sometimes in the gray substance.

Nine patients were considered immunologically stable, six did not contain enough data for analysis, and four were considered unstable. Plasma values of CD4 + T lymphocytes 6 months or more before encephalitis varied from 10/μL to 900/μL while admission values ranged from 84/μL to 1076/μL. Plasma values of CD8 + T lymphocytes before and at admission were normal except for one patient who in the 2 years before the encephalitis had levels of 853/μL to 7020/μL. Plasma viral load at admission ranged from 0 cp/mL to 65,800 cp/mL whereas in the cerebrospinal fluid ranged from 0 to 36,242 cp/mL.

Among the symptoms most commonly mentioned in the articles, 57.9% presented cognitive alterations and/or mental confusion, 47.4% headache, 36.8% convulsions, and 31.6% dizziness.

All 14 patients who underwent brain biopsy showed diffuse infiltration by CD8 + T lymphocytes, the majority with perivascular predominance, and 57.1% presented negative HIV-p24 protein and, when positive, was considered weakly positive.

It was possible to carry out the analysis of the plasma viral load and the CSF viral load of 11 individuals, of which seven (63.6%) presented higher levels in CSF than in the plasma.

Table 4a summarizes the data extraction of each individual and table 4b the MRI findings.

Discussion

Due to the small number of studies available, this systematic review was not able to generate a meta-analysis, but was able to summarize clinical and epidemiological data and suggest the magnetic resonance imaging and pathology findings, in addition to the available treatments and the outcome of the disease. Despite the cases series[5,11] identify a typical pattern of MRI alteration characterized by bilateral signal change in the FLAIR sequence and linear and multiple perivascular enhancement in MRI, only the case of Moulignier et al., 2013[1], and Moulignier et al., 2014[12], also showed contrast enhancement suggesting variations of presentation in the disease image, being necessary biopsy in some cases.

Drug immunosuppression with corticosteroids appears to be a good treatment option given the significant clinical improvement of the majority of patients, also having the option of combining mycophenolate. The treatment with only the exchange of cART reported by Morioka et al., 2016[7], suggests the resistance to antiretroviral treatment as a possible trigger for the development of the disease, while in other cases it was suggested as triggers the viral escape, minor infections, treatment with cART, and IRIS.

The finding of viral load in the CSF higher than in the plasma of some patients favors the hypothesis of viral escape as a trigger, even though the HIV-p24 protein is negative or weakly reactive. This mechanism has already been suggested in other cases reported in the literature, such as Canestri et al. 2010[14] and Rawson et al. 2012[15]. Most of the individuals analyzed in the studies included in this systematic review were considered to be immunologically stable by the authors suggesting the participation of antiretroviral treatment in the pathophysiology of the disease.

The similarities of CD8 + encephalitis with other neurological entities in HIV patients make their diagnosis often challenging and raises the question whether it is a distinct disease from the others or it is a spectrum of any of the diseases previously described in literature, among them IRIS, ADEM, HIVE, and diffuse infiltrative lymphocytic syndrome (DILS).

The study by Anthony et al. 2005[2] compared the brain pathology of HIV-positive individuals, with no evidence of neurological disorders, untreated with cART treated individuals evidencing an increase in microglia/macrophage activation levels similar to those found in HIVE subjects who did not use cART. In individuals used cART, perivascular and parenchymal in-

Table 4a. The data extraction of each individual

Patient	Age	Sex	I. stabil.	Entry way	Onset CD4+	Onset pVL (cp/mL)	CFS VL (cp/mL)	HIV-p24	MRI enhancement	Onset cART	Treatment	Outcome
1	46	Male	Yes	Minor infection	121	4500	NI	+	Yes	DDI 3TC IDVr	Corticosteroids	Death 9 months later
2	41	Male	Yes	Stop cART	120	35561	NI	+	Yes	Stop	Corticosteroids	Total recovery
3	36	Male	No	IRIS	93	0	0	+	Yes	DDI 3TC LPVr	Corticosteroids	Total recovery
4	47	Female	Yes	Minor infection	275	692	2236	+	Yes	LPV fAPVr T20	Corticosteroids	Death 3 months later
5	39	Female	No	IRIS	NI	NI	1120	–	Yes	DDI ABC ATVr	Corticosteroids	Death 9 months later
6	33	Female	NI	NI	283	2660	10300	–	Yes	FTC TDF ATVr	Corticosteroids	Death 12 months later
7	37	Female	Yes	Minor infection	495	65800	NI	–	Yes	ABC 3TC LPVr	Corticosteroids	Alive, cognitive impairment
8	54	Female	No	Minor infection	402	NI	672	–	Yes	None	Corticosteroids	Total recovery
9	33	Male	Yes	Escape	210	2379	1230	+	Yes	FTC TDF ATVr	Corticosteroids	Alive, cognitive impairment
10	43	Male	No	Escape	84	2765	36242	–	Yes	3TC ABC ATVr	Corticosteroids	Alive, cognitive impairment
11	35	Male	Yes	Minor infection	214	21700	1200	NI	Yes	AZT 3TC IDVr	Corticosteroids	Total recovery
12	59	Female	NI	NI	NI	NI	NI	NI	Yes	ABC 3TC LPVr	Corticosteroids	Death 1 month later
13	49	Male	Yes	Minor infection	114	200	3200	NI	Yes	LPV ABV 3TC	Corticosteroids	Alive, cognitive impairment
14	39	Male	Yes	NI	742	201	3294	NI	Yes	3TC ABC ATVr	Corticosteroids	Total recovery

(Continues)

Table 4a. The data extraction of each individual *(Continued)*

Patient	Age	Sex	I. stabil.	Entry way	Onset CD4+	Onset pVL (cp/mL)	CFS VL (cp/mL)	HIV-p24	MRI enhancement	Onset cART	Treatment	Outcome
15	27	Female	NI	Stop cART	175	23032	NI	–	Yes	RAL FTC, TDF	Corticosteroids	Clinical improvement with treatment, death after stop treatment
16	52	Male	NI	cART resistance	632	660	910	–	No	ATV TDF FTC RTV	Change of cART	Total recovery
17	52	Female	NI	Minor infection	220	0	NI	–	No	TDF FTC RTV ATV	Corticosteroids/ change of cART	Total recovery
18	34	Female	NI	Minor infection	1076	191	3383	NI	No	NI	Corticosteroids/ mycophenolate	Total recovery
19	52	Female	Yes	Minor infection	409	7500	72	NI	Yes	None	Corticosteroids	Total recovery

cART, combined antiretroviral therapy; IRIS, immune reconstitution inflammatory syndrome; MRI, magnetic resonance imaging; NI, not informed; CFS, cerebrospinal fluid; VL, viral load; pVL, plasma viral load.

filtrate by CD8 + was lower than in the cases of HIVE. The reported cases of CD8 + encephalitis in the literature until now show the activation of microglia/macrophages and increase of the CD8 + T lymphocyte infiltrate but, unlike the cases of HIVE, a strong reaction with the HIV-p24 protein or giant multinucleated cells is not observed, thus suggesting to be an entity distinct from HIVE.

DILS is described in patients with persistent lymphocytosis by CD8 + T lymphocytes who present visceral and salivary gland infiltration by CD8 + with HIV-p24 positive protein[16,17]. Despite having some similarities with CD8 + encephalitis in pathology and laboratory findings, the clinical presentation of these two diseases differ, and there was no report of salivary gland involvement in any of the reported cases of CD8 + encephalitis.

True demyelination foci were only found in one of the cases reported by Gray et al., 2013[11], and Lescure et al., 2013[5], favoring the distinction of CD8 + encephalitis from ADEM. The MRI contrast enhancement pattern found in the reported cases also differ from the enhancement pattern expected for ADEM that usually presents with complete or incomplete peripheral annular enhancement.

Gray et al.[11] and Lescure et al.[5] highlight the similarity of the pathological findings of CD8 + encephalitis with IRIS and suggest the hypothesis that immune reconstitution may generate an exaggerated response to latent active infection, a paradoxical immune response to a latent antigen or inactive infectious agent. Zarkali et al., 2016[13], also draw attention to the clinical-pathological similarity of IRIS to CD8 + encephalitis, concluding that these two entities overlap. Lescure et al., 2013[5], found an association of IRIS with CD8 + encephalitis in only two patients, which caused the hypothesis of IRIS as a possible trigger and not the same disease. The diagnostic criteria for IRIS are still no consensus, but in the histopathological study CD8 + lymphocytes predominate[11,18], making it difficult to distinguish from CD8 + encephalitis. IRIS cases without the identification of an infectious agent have already been reported[19,20] and could result from CD8 + encephalitis or an atypical form of IRIS presentation.

The impregnation pattern described by Gray et al[11]. and Lescure et al[5]. is very similar to the pattern found in chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) but, in these cases, there is a predominance of CD4 + T lymphocytes rather than CD8 + T lymphocytes[21].

Table 4b. The magnetic resonance imaging findings

Patient	Location and pattern	FLAIR hypersignal	Enhancement	Enhancement pattern	Post treatment MRI
1	Bilateral white and gray matter	Yes	Yes	Linear or punctate	NI
2	Bilateral white and gray matter	Yes	Yes	Linear or punctate	No enhancement and reduction of lesions in FLAIR
3	Bilateral white and gray matter	Yes	Yes	Linear or punctate	No enhancement and reduction of lesions in FLAIR
4	Bilateral white and gray matter	Yes	Yes	Linear or punctate	NI
5	Bilateral white and gray matter	Yes	Yes	Linear or punctate	NI
6	Bilateral white and gray matter	Yes	Yes	Linear or punctate	NI
7	Bilateral white and gray matter	Yes	Yes	Linear or punctate	No enhancement and reduction of lesions in FLAIR
8	Bilateral white and gray matter	Yes	Yes	Linear or punctate	No enhancement and reduction of lesions in FLAIR
9	Bilateral white and gray matter	Yes	Yes	Linear or punctate	No enhancement and reduction of lesions in FLAIR
10	Bilateral white and gray matter	Yes	Yes	Linear or punctate	No enhancement and reduction of lesions in FLAIR
11	Bilateral white and gray matter	Yes	Yes	Linear or punctate	No enhancement and reduction of lesions in FLAIR
12	Bilateral white and gray matter	Yes	Yes	Linear or punctate	NI
13	Bilateral white and gray matter	Yes	Yes	Linear or punctate	No enhancement and reduction of lesions in FLAIR
14	Bilateral white and gray matter	Yes	Yes	Linear or punctate	No enhancement and reduction of lesions in FLAIR
15	Tumefactive pattern in frontal lobe	Yes	Yes	Homogeneous	NI
16	Diffuse bilateral white matter involvement	Yes	No	-	NI
17	Diffuse and bilateral involvement of cerebral and infratentorial white matter and deep gray matter	Yes	NI	-	Reduction of subcortical white matter and deep gray matter lesions with near complete resolution of diffusion restriction areas
18	Bilateral white matter with mass effect and base nuclei	Yes	No	-	Stable injury with treatment and mass effect reduction
19	Brain white matter, caudate nucleus and intramedullary lesions	Yes	Yes	Punctate	No skull MRI. Persistence of intramedullary lesions but without contrast enhancement

MRI, magnetic resonance imaging; NI, not informed; FLAIR, fluid-attenuated inversion recovery.

Conclusion

The typical pattern of MRI alterations in the cases of CD8 + encephalitis was characterized by bilateral signal changes in the FLAIR sequence, in addition to linear and multiple perivascular impregnations after contrast. The biopsies showed microglial activation and reactive astrocytes with infiltration by T lymphocytes with the predominance of CD8 + T lymphocytes. Among the possible triggers of the disease were discontinuation of cART, viral escape, minor infections, and IRIS. The most commonly used treatment was corticotherapy, with the option of mycophenolate and the exchange of the cART regimen.

The magnetic resonance findings and also the pathology of CD8 + encephalitis cases described may resemble those described in IRIS, and our conclusion is that these two entities are indistinguishable from the available data. Despite this, some authors suggest that IRIS is only one of the triggers for CD8 + encephalitis and not the same entity. However, due to the paucity of CD8 + encephalitis cases available until now, new studies on the subject are necessary, mainly focusing on the attempt to elucidate the pathophysiology and etiology of CD8 + encephalitis, in addition to characterizing the differences between these two entities.

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