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Is the presence of an intrathecal synthesis of immunoglobulins associated with neurocognitive impairment in HIV-infected patients?

Etudiant
Badoux Thierry

Tuteur
Du Pasquier Renaud
Dpt de neurologie

Co-tuteur
Cavassini Matthias
Dpt de maladies infectieuses

Expert
Meylan Pascal
Dpt de maladies infectieuses

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Is the presence of an intrathecal synthesis of immunoglobulins associated with neurocognitive impairment in HIV-infected patients?

Thierry Badoux, Matthias Cavassini, Martina Rothenbühler, Samanta Simioni, R. Meuli, A. Berney, Giorgio E. Maccaferri, Deolinda Alves, Myriam Schluep, Renaud Du Pasquier

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INTRODUCTION

Worldwide, the incidence of HIV-associated dementia has decreased (1) However, the prevalence of HIV-associated neurocognitive disorders (HAND), mostly the milder forms, i.e. mild neurocognitve disorders (MND) and asymptomatic neurocognitive impairments (ANI) has increased in the combined antiretroviral therapy (cART) era (2). Indeed, 20% to 60% of well-treated HIV-infected patients, i.e. with undetectable HIV viremia, still present HAND in the cART era (3). HAND are characterized by psychomotor slowing, memory loss, and attention deficit (4). Possible explanations for this paradoxical phenomenon encompass: increased survival of HIV-infected patients thank to cART, low grade inflammation of the brain (5) insufficient penetrance of antiretroviral drugs through the blood brain barrier (BBB)(6), or on the contrary, toxic effect of some antiretroviral drugs (7, 8).

These somewhat contradictory hypotheses underline our poor understanding of HAND physiopathology. Here, we aim at determining whether the intrathecal synthesis of immunoglobulins G (IgG), hereafter referred as cerebrospinal fluid oligoclonal band (CSF OB), may help us in better understanding the immunopathogenesis of cognitive disorders. By analogy with other infection, such as syphilis or neuroborreliosis (9, 10), one can assume that, in the case of HIV-infected patients, the CSF OB are directed against HIV proteins (11). Nevertheless, in the case of HIV, the meaning of such CSF OB is unclear. Indeed, it is unknown whether this intrathecal inflammatory reaction is beneficial (viral control) or harmful (brain parenchyma destruction by the different inflammatory factors). Here, we looked at the association between CSF OB and cognitive disorders in HIV-infected patients, hypothesizing that if these CSF OB are protective, one should see an inverse correlation with the presence of cognitive disorders.

MATERIAL AND METHODS

Blood data and CSF samples were obtained from 73 patients who had been examined in the frame of the multidisciplinary Neuro-HIV platform of our Institution, between 2010 and February 2014. In this monthly platform, the patients underwent a one-day evaluation including a visit with an infectiologist (MC); a neurologist (also performing the lumbar puncture [RDP]), a neuropsychologist (SS), who performed a comprehensive 2-hour examination, assessing all cognitive fields that can be affected by HAND (12) and the functional autonomy, using the Instrumental Activities of Daily Living (IADL) Questionnaire (13); and a psychiatrist (GM, AB) who, looked for major psychiatric conditions, in particular depression using the MADRS scale (14). In addition, a brain MRI was performed to ensure that the lumbar puncture was feasible and to rule out CNS lesions. All patients signed an informed consent form according to the IRB of our institution.

We recorded the following parameters in the blood: albumin, HIV viral load, current and nadir CD4+ T cell count; and in the CSF: white blood cells, total proteins, albumin, and OB, using isoelectric focusing (15). In addition, the band profile in CSF was determined following the four consensus patterns (16), such as type 1: no bands in the serum nor in the CSF; type 2: presence of OCB only in the CSF; type 3: presence of OCB in both compartments, but with a predominance of bands in the CSF as compared to the serum; type 4: presence of OCB in both compartments identically. When a patient had a pattern 2 or 3, we substracted the number of bands in the serum from the number of bands in the CSF, thus obtaining the number of additional bands in the CSF.

Categorical variables were displayed as counts and percentages and were compared using the chi-squared test or Fisher's exact test where appropriate. Continuous variables are presented as median and interquartile range and the difference across groups was assessed using the Wilcoxon rank-sum test. We evaluated the influence of the explanatory variables on cognitive disorder using logistic regression. We applied both univariate models and a multivarite model. For the latter, we only considered variables that had a p-value < 0.200 in the univariate model. All hypotheses were two sided and p-value less than 0.05 was deemed statistically significant. We performed all statistical analyses with Stata (version 13.1).

RESULTS

Of the 73 patients who benefited from a full neuropsychological evaluation, 51 (70%) had cognitive disorders and 22 (30%) were normal. HIV infection was assumed to be the only cause of cognitive disorders in 16 patients (9 had ANI and 7 MND) (12). HIV infection was thought not to be the only etiology of cognitive disorders in 35 patients. In these 35 patients, contributing factors potentially affecting the cognition were mostly depression, less frequently alcohol abuse and past opportunistic infections. Most frequently affected domains were executive functions (88%), memory (78%), psychomotor slowing (68%), and attention (66%). This cognitive profile mainly corresponds to an impairment of subcortical functions, which is expected in HAND. Cortical functions were far less impacted; language dysfunction (12%), signs of apraxia (4%) and of agnosia (4%).

Brain MRI were normal in 30 patients (43%), 40 patients (57%) had lesions, and 3 had no data available. MRI considered as abnormal mostly showed cortico-sub-cortical atrophy and/or aspecific white matter spots. There was no unexpected finding such as tumor, abscesses, meningeal thickening, etc. Virorachia, i.e the number of copies of HIV in the CSF was detectable (>20 copies/ml) in 9/73 (12%) of patients.

We did not see blood or CSF differences between the patients with cognitive disorders and those without such disorders (Table1). We assessed the influence of the baseline characteristics displayed in Table 1 on the presence of cognitive disorder. We examined in particular the association between the number of oligoclonal band and the presence of cognitive disorders; this association was however not significant (p=0.127) in the univariate logistic model.

Table 1:

	Without cognitive disorder	With cognitive disorders	p-value
	N = 19	N = 54	
CD 4 nadir: median (IQR)	199.5 (139-211)	164.5 (33-262)	0.409
Current CD 4 count: median (IQR)	586 (449-685)	615 (396-785)	0.269
Viremia: median (IQR)	76 (72-220)	77 (34-180)	0.844
Virorachia : median (IQR)	2040 (2040-2040)	54.5 (39.8-517)	0.245
CSF WBC: median (IQR)	1 (0.7-3)	1 (0.5-2)	0.469
Total proteins: median (IQR)	455 (372-531)	446.5 (320-586)	0.753
Intrathecal synthesis present: n (%)	13 (72.2)	35 (66.0)	0.774
Profile of CSF IgG: n (%)			0.935
1	3 (16.7)	9 (17.3)	
2	8 (44.4)	21 (40.4)	
3	5 (27.8)	13 (25.0)	
4	2 (11.1)	9 (17.3)	
Nbr of additional CSF bands (n = 45) median (IQR)	11.5 (8-14)	9 (5-12)	0.110

Table 2: Univariate logistic regression

	Univariate	p-value
	OR (95% CI)	
CD4 nadir	0.99 (0.99;1.00)	0.811
Current CD4 count	1.00 (0.99;1.00)	0.289
Viremia	1.00 (1.00;1.00)	0.609
CSF WBC	0.91 (0.64;1.31)	0.635
CSF proteins_	0.99 (0.99;1.00)	0.815
Intrathecal synthesis	0.74 (0.23;2.43)	0.629
Profile of CSF IgG: n(%)		0.930
1	*Reference category*	
2	0.88 (0.19-4.08)	
3	0.87 (0.16-4.58)	
4	1.50 (0.81-11.24)	
Nbr_of additional CSF bands (n = 45)	0.90 (0.781; 1.03)	0.127

Next, we performed univariate logistic regressions on cognitive disorders (we did not perform a multivariate regression because just one p-value in the univariate regression were <0.200). We found that current and nadir of CD4+ T cell count, viremia, CSF white blood cells (WBC), CSF proteins, and the presence of an intrathecal synthesis were not associated whatsoever with cognitive disorder. However, additional bands seemed to have an impact on the prevalence of cognitive problems. Indeed, although it did not reach significance, there was a trend, in the

univariate analyses for an inverse correlation between the number of additional bands in the CSF and cognitive disorders.

DISCUSSION

In this work, we wanted to determine whether CSF OB are related to cognitive disorders in HIV-infected patients. We found that a large majority of HIV-infected patients do have CSF OB. The presence of CSF OB was well documented in the pre-cART era (17). Our study shows that this is still the case in well-treated patients. Reflecting the effectiveness of cART, 75% and 87% of our patients had undetectable HIV viral load in the serum and the CSF, respectively. We found no differences in terms of prevalence of CSF OB between patients with or without cognitive disorders. Next, we wondered whether the profile of CSF OB would differ between HIV-infected patients with or without cognitive disorders. Indeed, the profile of CSF OB is different depending on the underlying mechanism. In multiple sclerosis, type 2 is typical, which means that OB are found only in the CSF (18). By contrast, in inflammatory diseases that have a systemic component, one can find OB also in the serum, but in a lesser amount than in the CSF (Type 3, (18)). Using this read-out, we found no difference between patients with or without cognitive disorders. Since a large amount of patients had CSF OB, we next examined the intensity of the intra-thecal response. Thus focusing on those patients who had CSF OB (type 2 and type 3), we looked at the number of additional bands in the CSF as compared to the serum. Indeed, we hypothesized that the higher this number, the higher the intensity of the intra-thecal humoral immune response. We did not find significant differences between HIV-patients with or without cognitive disorders, however there was a trend for a higher number of CSF OB in patients without cognitive disorders, a finding which was present in the univariate (Table 1) and the multivariate (Table 2) analyses. In particular, every additional band lowered the probability of cognitive disorders ($p = 0.127$). Although these data must be taken with caution, it may suggest that the intrathecal humoral immune response may protect against neurocognitive impairment. Supporting this assertion, an earlier study found that anti-Tat antibodies in the CSF were inversely correlated with the presence of HIV-associated neurocognitive disorders, suggesting that these antibodies were protective (19). Of interest, even if these data were not significant, they were by far those that were the closest to significance as compared to all other examined parameters.

This study has strengths and weaknesses: the neuropsychological evaluation was thorough, performed by a skilled neuropsychologist (SS) with a good knowledge of HIV-associated neurocognitive disorders. However, although all patients were HIV-infected, the cause of cognitive disorders was often mixed, attributable not only to HIV, but also to concomitant factors, the psychiatric ones being the most frequent. These mixed etiologies of cognitive disorders may have attenuated the effects we were looking at. Second, there was a high prevalence of cognitive disorder among our patient (70%), which is explained by the setting of our neuro-HIV plateform to which mostly patients complaining of cognitive disorders are referred. Although this remains speculative, one can imagine that with a larger number of HIV-infected patients without cognitive disorders, the inverse correlation between additional bands in the CSF and cognitive disorders may have been significant.

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METHODE :

Une grande partie des données de notre étude à été faites sur la base de la plateforme Neuro VIH, CHUV. Ouverte depuis 2010, cette plateforme ce tient mensuellement et a été ouverte pour investiguer de manière pluridisciplinaire des patients HIV+ se plaignant de troubles neurologiques divers et variés. La majorité des plaintes étant des troubles cognitifs.

Cette plateforme a permis de comptabiliser 73 patients dans notre étude.

Chaque patient inscrit à cette plateforme a passé une journée entière au CHUV, pour y suivre différents examens, et y a donné son plein consentement.

-Arrivée le matin à jeun

-Prise de sang (Taux de Leucocytes / CD4 nadir / virémie / isoélectrofocalisation des bandes Ig G / Albumine)

Puis dans un ordre aléatoire :

-Consultation d'un infectiologue spécialisé dans le HIV.

-Consultation psychiatrique, s'intéressant particulière au pendant dépressif des patients en utilisant l'échelle MADRS.

-Consultation neuropsychologique , incluant une investigation détaillé de tous les domaines cognitifs de chaque patient, ainsi que de leur autonomie fonctionnel se basant sur le questionnaire IADL (Instrumental Activities of Daily Living). Les domaines cognitifs investigués étaient les suivant : Vitesse psychomoteur, attention, mémoire, fonctions exécutives, langage, apraxie agnosie et capacité moteur.

-Consultation Neurologique

-IRM cérébral, afin d'exclure une éventuelle cause expansive des troubles neurologiques (Masse, hypertension intracrânienne, hémorragie…), mais également de mettre en évidence les lésions de la substance blanche, ou grise, ainsi que les différentes atrophies.

-PL (Albumine / virorachie / protéinorachie / isoélectrofocalisation des bandes IgG intra-thécale) Il faut noter que tous les patients n'ont pas toujours accepté la PL, ou que celle-ci fut impossible à faire chez certains, ou encore qu'elle fut faites, préalablement, dans un autre établissement.

La mise en évidence d'une synthèse intra-thécale ce fait par la comparaison de l'isoélectrofocalisation des IgG oligoclonaux sanguin et ceux du LCR.

Les différents types de bandes oligoclonalles possibles sont les suivant.

1) S- / L- (Absence de bande dans le sérum sanguin ainsi que dans le LCR)

2) S- / L+ (présence de bandes seulement dans le LCR)

3) S+ / L++ (les mêmes bandes sont présentes et dans le sérum et dans le LCR, cependant des bandes **additionnels sont** retrouvés dans le LCR)

4) S+ / L+ (**mêmes** bandes retrouvées dans le sérum et le LCR

Le pattern 2 et 3 dénote d'une synthèse intrathécale. Dans ces 2 derniers cas, nous avons soustrait le nombre de bandes oligoclonalles du sérum à celui du LCR, afin de compter le nombre de bandes additionnels exacts.

Les diagnostics relevés pour cette étude, sont basés sur le rapport neuropsychologique, et permettent de séparer les patients en 2 catégories :

-Présence de troubles cognitifs.

-Absence de troubles cognitifs.

L'imagerie et la consultation de psychiatrie permet de savoir si d'autres étiologies peuvent expliquer les plaintes neurologique du patient. Ou si seul le VIH en est la cause.

Méthode statistique:

Les variables catégorielles ont été affiché en pourcentage et ont été comparé entre eux grâce à un Chi-squared test ou un test de Fisher lorsque ce dernier était approprié. Les variables continues ont permis de mettre en évidence la médiane et les écarts interquartiles, la différence entre les groupes ont été calculés en utilisant le Wilcoxon rank test. Nous avons évalué l'influence des variables qualitatives sur les troubles cognitifs à l'aide de régression logistique. Nous avons utilisé le model univarié ainsi que le model univarié. Pour le second, nous avons seulement considéré ées variables qui avaient un p-value de <0.200 dans le model univarié. Toutes les hypothèses ont été analysé par 2 reprises, et seul les p-value au-dessous de 0.05 sont considéré comme statistiquement signifiant. Toutes les analyses statistiques ont été faites à l'aide du programme Stata (version 13.1).

RESULTATS!

Sur les 73 patients qui ont bénéficié d'une pleine et entière investigation neurologique, 51 (70%) avaient des troubles cognitifs et 22 (30%) étaient sains d'un point de vue cognitifs , ce qui est très important, mais qui semble logique étant donné que les patients de la plateforme n'y ont recours que lorsqu'ils n'ont des plaintes neurologiques. Le VIH était le seul facteur étiologique de ces troubles chez 6 patients seulement. (9 ANI et 7 MND, 0 HAD), dans le reste des cas, c'est à dire chez 35 patients l'étiologie des troubles semblaient multifactorielles. Parmis les différents autres facteurs pouvant causer les troubles cognitifs la dépression revenait

fréquemment, ainsi que les abus de substances tel que l'alcool ou les drogues psychoactives, on trouve aussi quelques séquelles d'infection neurologique opportuniste lié au VIH, tel que la toxoplasmose cérébrale pour n'en citer qu'un.

Les domaines de cognition le plus souvent atteint chez les patients furent les fonctions exécutives (88%), la mémoire (78%), la psychomotricité (68% de ralentissement) et l'attention (66%). Ces profils cognitifs correspondent bien au profil attendu chez les patients avec une dysfonction sous-corticale tel que c'est le cas dans les troubles cognitifs lié au HIV. Les fonctions corticales ont été beaucoup moins touchés : un dysfonctionnement du langage n'était présent que chez 12% des patients, l'apraxie ou l'agnosie chez seulement 4%

Concernant l'imagerie, l'IRM cérébral était normal chez 30 patients (43%) alors que 40 patients (57%) présentaient des lésions, principalement des atrophies cortico-sous-corticales ainsi que des lésions focales aspécifiques de la substance blanche. Il n'y a eu aucun patient présentant des masses pathologiques tels que des tumeurs ou des abcès ni des effets de masses dû à une hémorragie quelconques. Aucun patient ne présentait de signe de méningisme (épaississement méningé). A noter que 3 patients n'avaient pas de données disponibles.

Pour ce qui est des ponctions lombaires, la virorcahie (nombres de copies du HIV dans le LCR) était détectable (>20 copies/ml) chez 9 patients sur 73 (12%). Nous avons évalué l'influence des caractéristiques de base affichées dans le tableau 1 sur la présence de troubles cognitifs, il n'y avait aucune différence statistiquement significatif sur les différents marqueurs du LCR entre les patients avec ou sans troubles cognitifs, les analyses sanguines n'ont non plus pas relevé de différence (TABLE 1). Nous nous sommes penché en particulier sur l'association du nombre additionnels de bandes oligoclonaux entre le sang et le LCR et les troubles cognitifs, cette association n'est malheureusement pas significative (p=0.127), dans le model univarié du moins.

Table 1:

	Without cognitive disorder	With cognitive disorders	p-value
	N = 19	N = 54	
CD 4 nadir: median (IQR)	199.5 (139-211)	164.5 (33-262)	0.409
Current CD 4 count: median (IQR)	586 (449-685)	615 (396-785)	0.269

Viremia: median (IQR)	76 (72-220)	77 (34-180)	0.844
Virorachia : median (IQR)	2040 (2040-2040)	54.5 (39.8-517)	0.245
CSF WBC: median (IQR)	1 (0.7-3)	1 (0.5-2)	0.469
Total proteins: median (IQR)	455 (372-531)	446.5 (320-586)	0.753
Intrathecal synthesis present: n (%)	13 (72.2)	35 (66.0)	0.774
Profile of CSF IgG: n (%)			0.935
1	3 (16.7)	9 (17.3)	
2	8 (44.4)	21 (40.4)	
3	5 (27.8)	13 (25.0)	
4	2 (11.1)	9 (17.3)	
Nbr of additional CSF bands (n = 45) median (IQR)	11.5 (8-14)	9 (5-12)	0.110

Table 2: Régression logistique univariée

	Univariate	p-value
	OR (95% CI)	
CD4 nadir	0.99 (0.99;1.00)	0.811
Current CD4 count	1.00 (0.99;1.00)	0.289
Viremia	1.00 (1.00;1.00)	0.609
CSF WBC	0.91 (0.64;1.31)	0.635
CSF proteins_	0.99 (0.99;1.00)	0.815
Intrathecal synthesis	0.74 (0.23;2.43)	0.629
Profile of CSF IgG: n(%)		0.930
1	*Reference category*	
2	0.88 (0.19-4.08)	
3	0.87 (0.16-4.58)	
4	1.50 (0.81-11.24)	
Nbr_of additional CSF bands (n = 45)	0.90 (0.781; 1.03)	0.127

Ensuite nous avons effectué une régression logistique univariée sur les troubles cognitifs (notez que nous n'avons pas effectué de régression logistique multivariée étant donné que seul 1 p-value était au-dessous de <0.200 dans la régression univariée).

Nous avons trouvé que les Cd4 actuels et Nadir, la virémie, les leucocytes dans le LCR ainsi que la protéinorachie et la synthèse intrathécalle d'IgG n'étaient en aucun cas associé aux troubles cognitifs. Cependant si on cherche en détail dans la synthèse intrathécal, et que l'on s'intéresse à l'importance de cette synthèse en comptant le nombre de bandes additionnelles dans le LCR et les troubles cognitifs, il apparaît une tendance statistique, non significative en revanche. La tendance montre que plus la synthèse intrathécale est importante (=plus il y a de bande additionnel) moins il y a de trouble cognitif.