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CNS Immunoactivation and Neuronal Damage in Patients with Progressive Neurocognitive Impairment

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Background

Although HIV-associated neurocognitive disorder (HAND) remains prevalent, and the presence of HAND may increase the risk of symptomatic progression in neurocognitive impairment, it is not fully established if HAND, or HAND progression represents an ongoing pathologic process in the CNS of patients responding well to antiretroviral therapy (ART)

Purpose

We investigated if milder forms of HAND, or HAND disease progression were associated with axonal injury (measured by CSF NFL) or intrathecal immune activation (measured by CSF neopterin) in virally suppressed patients on ART

Study design

We identified subjects on ART with plasma HIV-1 RNA <50 c/mL without significant confounding conditions (e.g., current substance dependence) cross-sectionally from longitudinal studies (CHARTER and HNRC). Subjects had undergone neurocognitive performance (NP) testing and CSF sampling on two separate occasions to evaluate NP stability and change in CSF biomarkers, and were classified as NP normal (NPN) or neurocognitively impaired (NCI) based on NP test result. The NCI group included subjects with asymptomatic neurocognitive impairment (ANI) or mild neurocognitive disorder (MND). NP change was determined in relation to published normative standards

Method

CSF concentrations of NFL were measured by enzymatic 2-site quantitative immunoassay (UmanDiagnostics, Umea, Sweden). CSF neopterin was measured by ELISA. Analyses involving repeated measurements were performed with linear mixed effects models

Results

Cross-sectional analysis

- No significant difference in age-adjusted CSF NFL in patients with NCI or NPN
- CSF neopterin was 25% higher in the NCI group (p=0.04)
- A correlation was found between CSF NFL and neopterin in the NCI-group (r=0.30; p=0.0003) but not in the NPN group (r=-0.13; p=0.3)

Prediction of progression

- No significant difference in CSF NFL between subjects with stable or declining NP test result
- CSF neopterin was 28% higher in subjects with NP decline (p=0.02)
- No difference in CSF biomarker change (Δ NFL or Δ neopterin) between study groups

3. CSF Neopterin

Figure 1
Values are $\log_{10}$ transformed for presentation. (**A.**) Baseline median (IQR) CSF NFL was 487 (371-687) ng/l in the NP stable group and 555 (347-744) ng/l in the NP decline group. Follow up median (IQR) CSF NFL was 480 (388-678) ng/l in the NP stable group and 536 (320-735) ng/l in the NP decline group
(**B.**) Baseline median (IQR) CSF neopterin was 7.7 (4.9-13) nmol/l in the NP decline group and 6.2 (4.7-8.9) nmol/l in the NP stable group. Follow up median (IQR) CSF neopterin was 6.3 (4.9-13.6) nmol/l in the NP decline group and 5.4 (4.7-8.7) nmol/l in the NP stable group. Dotted line represents upper normal reference for neopterin (5.8 nmol/L)

Conclusions

- **Mild HAND (ANI and MND) was associated with a higher degree of intrathecal immune activation measured as CSF neopterin**
- **CSF neopterin was higher in subjects with neurocognitive decline, suggesting that neurocognitive impairment may represent a clinically significant pathologic process within the CNS despite suppressive ART**
- **The correlation found between CSF NFL and neopterin indicates an association between immune activation, axonal damage and neurocognitive impairment during effective ART that needs to be further characterized in prospective studies**

Table 1. Baseline characteristics	Cross-sectional		Progression	
Subject group	NPN (n=29)	NCI (n=70)	NP stable (67)	NP decline (32)
Age	45 (39-53)	48 (42-55)	47 (42-54)	46 (41-50)
Male sex (%)	26/29 (90%)	64/70 (91%)	60 (90%)	30 (94%)
Nadir CD4, median (IQR) cells/mm^3	120 (10-274)	64 (10-206)	70 (9-232)	71 (15-208)
Current CD4, median (IQR) cells/mm^3	602 (453-899)	503 (334-685)*	545 (360-788)	476 (342-668)
Undetectable in plasma, median (IQR) days	783 (354-1689)	382 (0-1084)*	409 (164-1252)	374 (0-767)
Current major depression, n (%)	2/25 (8%)	7/65 (11%)	5 (7%)	4 (13%)

*No significant differences between groups, except * (p<0.05)*

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