A case of Cerebrospinal fluid HIV RNA Escape Syndrome

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SUMMARY

A 54-year-old man, with treated Human Immunodeficiency Virus (HIV) presented with a sub-acute deterioration of speech, mobility and cognition. Analysis of cerebrospinal fluid (CSF) revealed a raised protein and a discordant CSF HIV RNA paired with plasma HIV RNA, confirming the diagnosis of CSF HIV RNA escape syndrome. This report analyses the presentation of this syndrome and highlights the importance of considering this diagnosis in people with treated HIV with new neurological symptoms.

BACKGROUND

This report describes a case of CSF HIV RNA Escape Syndrome. This is defined as evidence of discordant HIV replication in the CSF despite low or undetectable HIV RNA in plasma(1).

The mechanism for this syndrome is compartmentalisation of the virus within the CNS resulting in discordant replication. Typically, HIV disseminates into the CNS early in infection and replicates in microglia and astrocytes causing both direct and indirect neuronal injury. In the UK, HIV is a chronic disease with 98% of people with HIV (PWH) treated with combination antiretroviral therapy (cART), with 98% achieving viral suppression to 'undetectable' levels (typically <50 copies/mL) within both CSF and blood compartments(2). However, in some cases, despite the peripheral suppression of the virus, HIV can evolve independently within the CNS, becoming compartmentalised(3). There have been several identified risk factors for this, including: HIV drug resistance, low nadir CD4 count, longer duration of HIV infection, low level viraemia and protease-inhibitor therapy (4–6).

Typically, patients may present with subacute onset of one or more deficits involving sensory, motor or cognitive function (4)(7). One study noted the most frequent presenting symptoms have been reported as: cognitive decline, confusion and headache(8).

Although, it is a rare clinical condition, studies report the prevalence ranging from 4 to 20%(9,10) in PWH, with the condition defined as the presence of quantifiable HIV RNA in the CSF at any level, when plasma HIV RNA is suppressed(11). However, this prevalence has been questioned given the biased nature of published populations. Two large studies from Europe and USA of virally suppressed patients who systematically underwent lumbar puncture as part of research studies reported the prevalence between 1-2%(12,13).

A CSF sample demonstrating HIV replication in the presence of a normal plasma viral load is diagnostic. A high protein and high white cell count in CSF are supportive of the diagnosis but non-specific. However, routine testing in asymptomatic patients has not been recommended(9). Brain imaging has been demonstrated to show diffuse white matter signal abnormalities in T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences on magnetic resonance imaging (MRI)(14). These features have been reported to be present in 50-90% of people with symptomatic CSF HIV RNA escape(8,14).

The mainstay of treatment involves sequencing plasma and HIV RNA to look for drug resistance mutations and optimising combination antiretroviral therapy (cART) considering antiretroviral history, documented resistance mutations (both recent and historic) and antiretroviral pharmacokinetics.

CASE PRESENTATION

A 54-year-old male patient with a background of chronic HIV infection, reported progressive balance problems and orthostatic dizziness over months, as well as a general decline in cognition and slurred speech. A recent attendance to the emergency department had been noted a few months previously, where he had had a fall against a wall due to unsteadiness. On that admission, examination findings included mild slurred speech, new upward nystagmus, and lateral gaze palsy. After a normal CT-head, the patient left the department against medical advice. The patient had had a significant deterioration in his mood and was becoming increasingly impatient evident from several 'did not wait' and 'did not attend' appointment outcomes and discharging against medical advice. Consequently, clinical management was challenging.

The patient was diagnosed with HIV in 2003 and had been intermittently adherent with combination therapy. There were a few blips to his viral load and resistant mutations over recent years including dual class resistance to nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) with M184V, K103N and L100I mutations, resulting in changes to cART. The most recent CD4 count was 960 cells/mm^3 (normal range >500 cells/mm^3), viral load <50 copies per ml (undetectable) on a single-tablet combination of tenofovir alafenamide, emtricitabine, darunavir and cobicistat (Symtuza). Other relevant medical history was emphysema, anxiety, and depression. Medications included Symtuza once daily, sertraline 100mg once daily and Anoro Ellipta inhaler 55/22. The patient worked as a cleaner, smoked 10 cigarettes per day and had an alcohol intake of approximately 25 units per week. He had a long-term, sero-concordant (HIV-positive) partner.

On examination there were no abnormalities in the cardiovascular and respiratory systems. Abdominal examination was normal. He was alert and orientated and was able to tell his own story but had a severe cerebellar dysarthria, sustained up-gaze nystagmus and mild limb and gait ataxia.

INVESTIGATIONS

A blood panel was taken, and a full blood count showed a normal haemoglobin with raised but longstanding mean corpuscular volume of 105fL (normal range 80-100fL). Other bloods, including urea and electrolytes, liver function tests, coagulation screen, bone profile, c-reactive protein vitamin B-12 and folate were within normal range. Syphilis screen was negative and plasma HIV RNA was undetectable.

Magnetic Resonance Imaging (MRI) of the brain was reported as showing non-specific small white matter hyperintensities in the temporal lobes and a degree of generalised parenchymal atrophy, more marked than expected for age, allowing for significant movement artefact (figure 1).

A lumbar puncture was performed; CSF had a clear appearance with a red blood cell count: 0 $x10^{x6}$/L. white blood cell count: 7 $x10^{x6}$/L, protein 1.42g/L (normal range 0.15 to 0.45g/L), glucose 3.2mmol/L (2.2 to 3.9mml/L, blood 6.2 mmol/L). No organisms were seen on gram stain and there was no growth on culture. CSF viral RNA: 8,574 copies/mL with paired plasma HIV RNA of 121 copies/mL.

Viral genotyping was successful on the plasma sample despite the low viral load and no resistance mutations were detected. However, in the CSF, M184V and T215TA resistance mutations were present, indicating differential evolution of HIV in the CNS as well as high-level resistance to emtricitabine component of his cART. HIV was R5 tropic both plasma and CSF indicative of susceptibility to maraviroc.

TREATMENT *If relevant*

Following confirmation of CSF HIV RNA escape syndrome; the patient was empirically commenced on maraviroc and dolutegravir in addition to continuing the combination tablet whilst awaiting tests of viral resistance genotyping. These medications were expected to be active, have a higher genetic barrier to resistance and have favourable pharmacokinetic parameters with expected penetration in the CNS. Further CSF genotyping showed resistance to nucleoside reverse transcriptase inhibitors; including high level resistance to emtricitabine and lamivudine, medications were continued with a good clinical response.

OUTCOME AND FOLLOW-UP

The patient slowly improved in terms of cognition and gait. A few weeks following changes in cART; he was admitted to hospital for a few days following another fall. The admitting team were concerned for an encephalitis so repeated a lumbar puncture to assess for this; red blood cell count: 1 $x10^{x6}$/L. white blood cell count: 10 $x10^{x6}$/L, 100% lymphocytes, protein: 1.0g/L (0.15 to 0.45g/L), glucose: 3.2mmol/L (2.2 to 3.9mml/L). No organisms were seen on gram stain and there was no bacterial growth on culture. CSF HIV RNA was 62 copies/mL paired with an undetectable plasma level. He was closely followed-up by the infectious diseases team monthly to review his response to the new regimen.

DISCUSSION

The onset of symptoms occurred approximately 6 months before being diagnosed with CSF HIV RNA escape syndrome. The delay was multifactorial. This is a rare condition with a broad presentation and the variable engagement with healthcare services. Retrospectively, the agitation and poor compliance may have been associated with his clinical presentation of CSF HIV RNA escape. He also had focal but non-localising signs, such as an upward gaze palsy and ataxia. The MRI, allowing for movement artefact particularly in the FLAIR sequence, showing white matter signal abnormalities were again non-specific, but significant in the context of the diagnosis. The most common finding on MRI is diffuse white matter signal abnormalities; involving multiple regions of supra- and infratentorial regions(14).

The patient in this case had several identifiable risk factors, namely; previous HIV resistance, intermittent concordance of medications and over a decade of HIV infection(4–6).

Optimisation of antiretroviral medications is key to the management of CSF HIV RNA escape. The central nervous system penetrance (CPE) score has historically been used to identify the most effective cART to cross the blood-brain barrier to control CNS infection. A higher score correlates with a higher penetrance of the CNS(15). However, this scoring system has been called into question and its use is not recommended by the British HIV Association which favours modifications to cART based on paired plasma and CSF genotypic results(16,17). The treatment response, reflecting the onset, is a slow process that requires strict adherence and monitoring of intensive, targeted cART.

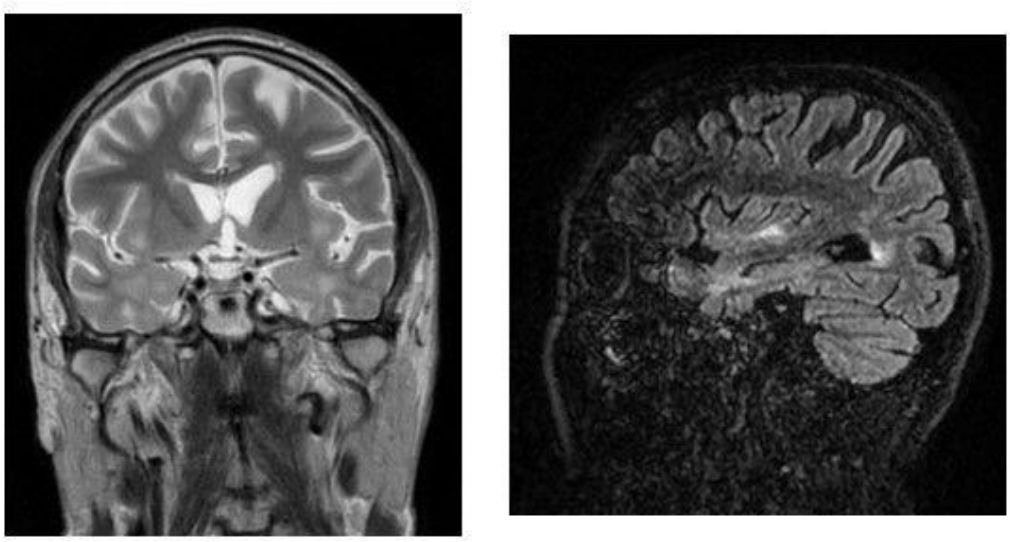

Figure 1 T2 coronal and Sagittal FLAIR MRI

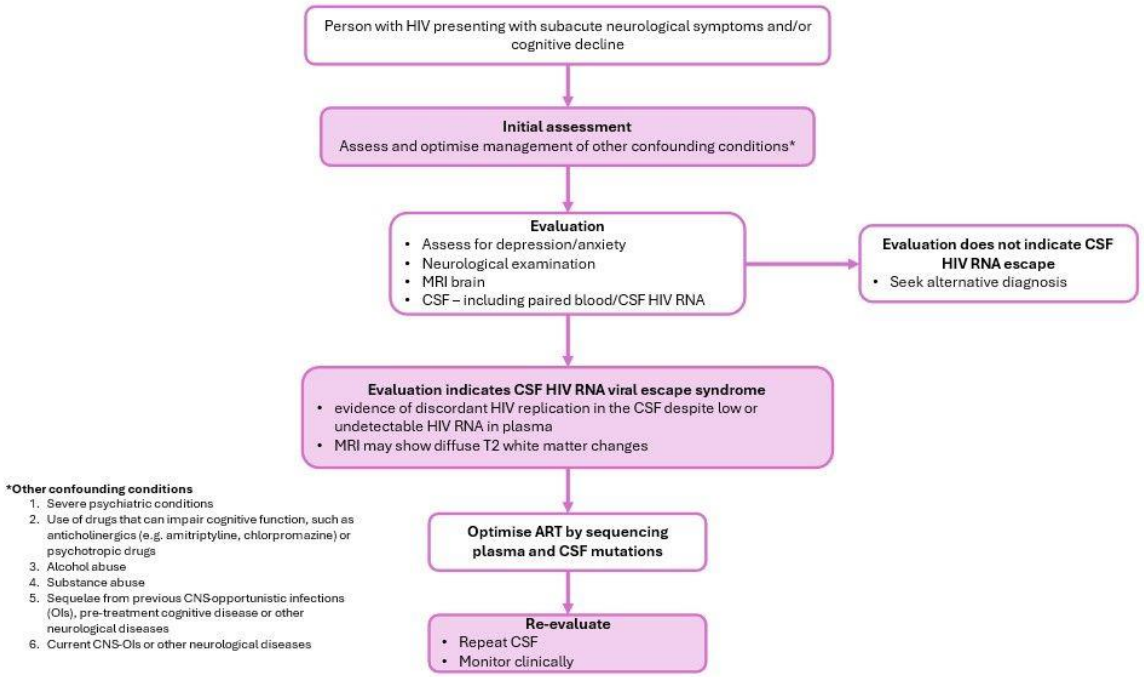

Figure 2 Flow chart summarising the diagnosis and management of CSF HIV RNA escape syndrome, adapted from EACS (18)

LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*

- In the presence of acute and chronic neurological symptoms in people with treated HIV CSF HIV RNA escape syndrome should be considered.
- Paired plasma and CSF HIV RNA +/- genotyping are key to the diagnosis and require specialist laboratory testing
- The mainstay of management is optimising antiretroviral treatment based on genotypic resistance results and antiretroviral history (figure 2(18))

Further reading

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Competing interests

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SN wrote the collated, drafted and edited subsequent revisions of the paper. JU assisted in the draft, edited multiple revisions and gave specialist input and advice. TH edited draft and revisions, gave specialist input and advice. Thanks to Dr Mouhammed Dally, who assisted with finding radiographic imaging.

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Legends

Figure 1 T2 coronal and Sagittal FLAIR MRI images

Figure 2 Flow chart summarising the diagnosis and management of CSF HIV RNA escape syndrome, adapted from EACS (18)