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New Insights into immune Reconstitution Inflammatory Syndrome of the Central Nervous System

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Abstract

Purpose of review—To highlight the importance of immune reconstitution inflammatory syndrome (IRIS) affecting the brain in HIV-infected individuals in the absence of opportunistic infections. To describe the varied clinical manifestations, unifying pathophysiological features and discuss the principles of management of this syndrome.

Recent Findings—IRIS within the brain is commonly seen in patients with HIV infection upon initiation of antiretroviral drugs. The fulminant forms occur in the face of opportunistic infections or uncontrolled viral replication within the brain. In this case the enhanced immune response is targeted against the microbial agent, and the brain suffers bystander damage. Treatment requires the combination of the antimicrobial agent, continued antiretrovirals and in some cases corticosteroids. It is increasingly being recognized that despite adequate control of viral replication in the brain some patients develop a chronic form of T cell encephalitis which appears to be driven by continued production of HIV-Tat protein. In others the immune response may be targeted against the host antigens in the brain.

Summary—In patients with CNS-IRIS the use of corticosteroids and strategies that prevent T cell migration into the brain may be needed. Extreme caution is necessary if viral eradication strategies are to employed that involve activation of viral reservoirs, since these patients may be at risk for developing CNS-IRIS.

Keywords

Brain; antiretrovirals; HIV associated neurocognitive disorders; Tat; encephalitis

Introduction

The availability of antiretroviral therapy (ART) has dramatically changed the face of the Human Immunodeficiency Virus (HIV) pandemic with a major improvement of life expectancy. However at the same time, it was realized that some patients with HIV infection develop a paradoxical worsening of clinical status after the initiation of ART. This has been termed Immune Reconstitution Inflammatory Syndrome (IRIS) (1-3). As the viral load diminishes and the immune system recovers, patients may develop immune pathology either

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in the periphery or in the central nervous system (CNS). While the term IRIS has been used to describe the more severe form of inflammation, and is thereby recognizable from clinical signs, it is becoming increasingly apparent that IRIS is a spectrum disorder and may range in severity and chronicity. All patients with HIV infection managed with ART undergo acute immune dysregulation and chronic inflammation and immune dysfunction (4, 5) that may contribute to HIV associated pathologies such as stroke (6), autoimmunity (7, 8), HIV-associated neurological disorders (HAND) (9, 10), cancer (11, 12) and premature aging (13-15).

Understanding the consequences of immune reactivation in the context of HIV infection has taken up new importance since current strategies for viral eradication (16, 17) include several drugs that would activate viral reservoirs with the hope that cytotoxic immune responses would then eradicate the reservoirs (18, 19). Driving further immune activation in patients with chronic aberrant immune function may actually trigger IRIS or IRIS-like clinical conditions which may be particularly devastating given the extent of CNS HIV infection (20). Any eradication strategy should prepare for this potential complication.

Incidence of IRIS and CNS-IRIS

A meta-analysis of 17 cohorts not restricted in the type of IRIS, estimated an IRIS incidence ranging from 3-39% (21). Retrospective studies from Mexico (22) and Mozambique (23) of 390 and 136 patients respectively initiating ART indicate that the incidence of IRIS is approximately 27%. The vast majority of IRIS cases are associated with opportunistic infections (OI) either recognized prior to initiation of ART but worsening after therapy (paradoxical IRIS) or recognized after therapy initiation due to the restoration of the immune system (unmasking IRIS) (Figure 1). The overall incidence of CNS-IRIS inclusive of all patients initiating ART is estimated to be approximately 1% (24). However, similar to IRIS, CNS-IRIS often occurs within the context of an OI and therefore the incidence of CNS-IRIS is frequently assessed in populations with a particular OI. Thus the incidence of CNS-IRIS is highly variable, averaging 15-25% and ranging upwards of 40% in high-risk individuals (25-29**). A study of 110 consecutive patients with HIV and a diagnosed CNS OI demonstrated the occurrence of CNS-IRIS to be 16.4% (29**). Similarly, a study of 620 patients admitted to hospital with new or worsening neurological disease and HIV demonstrated an overall CNS-IRIS incidence of 11.8% (26); however 40% of patients with CNS tuberculosis in this cohort developed CNS-IRIS. The wide range in incidence of CNS-IRIS reflects diagnostic challenges and regional resource availability, but also may represent biological consequences related to specific pathogen associations and disease mechanisms.

IRIS: Mortality and Risk Factors

IRIS is now recognized as a significant cause of morbidity and mortality in the HIV-managed population. IRIS is associated with an increased risk of mortality (mortality ratio of 2.3) and hospitalization (three fold risk) after adjusting for confounding factors (22). Similar trends in mortality were found in another adult (23) and a pediatric cohort (30*). While CNS-IRIS is a smaller proportion of all IRIS cases, it represents the most debilitating form of IRIS and is associated with death or permanent neurological deficit in an estimated

16-50% of cases (27, 29**, 31, 32). The CD4 nadir, an indicator of the degree of immune suppression, and the presence of an OI at the time of initiation of ART are the greatest risk factors for the development of IRIS (3, 22, 33). A reduced body mass index was also independently associated with the development of IRIS in two separate cohorts; however occurrence of CNS-IRIS was not included in the analysis (22, 23).

CNS-IRIS in association with Opportunistic Infection

A hallmark of CNS-IRIS is the infiltration of the CNS with activated T-cells. Many factors may drive the immune response during IRIS; however the majority of CNS-IRIS cases are associated with an OI. Although ART has contributed to a reduced incidence of CNS OI (29**), OI within the CNS are potent immune stimulators for the restoring immune system and the limited physical space of the brain predisposes it to damage from edema during inflammatory events. Several pathogens are associated with the development of CNS-IRIS but *Mycobacterium tuberculosis* (25, 34**, 35), *Cryptococcus neoformans* (34**, 36, 37) and JC virus (38-40) account for the majority of CNS-IRIS incidents. The clinical features, estimated rates of IRIS occurrence and risk factors associated with these infections were recently reviewed by Bahr and colleagues (34**). Other opportunistic infections, such as Varicella Zoster Virus (41-43), Cytomegolovirus (44, 45), Candida species (46) and *Toxoplasma gondii* (47-49) are associated with CNS-IRIS, but contribute to the frequency of disease at much reduced rates as compared to cryptococcal meningitis (CM) and tuberculosis (TB) infections. Studies on the prevention of CNS-IRIS suggest that a one-size-fits-all approach is not appropriate once a patient is immune compromised. Ideally, early detection of HIV infection through routine screening would enable initiation of therapy before CD4+ T cell counts are below 500 (50), or if resources are available, immediately after diagnosis of HIV infection. By preventing the immune system from becoming compromised some of the risk of immune dysregulation and IRIS are avoided. If HIV infection is diagnosed in patients who are already immune compromised, careful screenings for CNS-OI prior to ART initiation should be completed. Reducing the antigenic burden within the CNS may help prevent adverse neurologic inflammation. Delaying ART for five weeks to first treat CM has been shown to improve survival although there was no statistically significant difference in occurrence of CNS-IRIS (early ART = 20% IRIS, delayed ART = 13% IRIS) (51**). In contrast, it is essential to begin ART immediately if JCV infection is detected within the CNS regardless of the risk of IRIS as the immune system is the only current defense against this pathogen and corticosteroids have shown some benefit if CNS-IRIS does occur (39, 40). In a study of immediate versus delayed ART in 806 patients with TB, 61 patients developed IRIS of which four developed CNS-IRIS. Of these four patients, 75% received early ART and 25% received delayed ART (52*). In the case of tuberculosis meningitis (TBM) delaying ART reduced the most severe adverse clinical events but did not impact mortality (53). Therefore, it is currently recommended that in the case of TBM ART be delayed four weeks (34**).

CNS-IRIS and HIV encephalitis

Although not considered an OI, residual or untreated HIV replication within the CNS may lead to HIV encephalitis (HIVE) and may also contribute to the development of CNS-IRIS

and chronic inflammation. IRIS is distinct from neurological complications associated with viral replication in the CNS and therapy failure, although clinically the presentation may mimic IRIS and may involve inflammation (54, 55). Elevated CNS viral loads, even in the presence of reduced viral loads in the periphery, may result not only in CNS inflammation but also in neurotoxicity and neurodegeneration from viral products (56-59). Reduction of CNS viral loads through increasing ART CNS penetration can lead to improved neurological status (9, 60*, 61) therefore it is important to assess if the CNS is not virally suppressed. Other reports suggest that ART and long-term higher CNS penetrating ART regimes may be associated with neurologic damage and increased risk of HAND (62-64*), however during frank CNS viral replication controlling the virus and thereby reducing neurotoxicity and inflammation within the CNS, is imperative.

IRIS in the absence of Opportunistic Infections

CNS-IRIS can occur in the absence of OI and these cases may be extremely informative on the mechanism of IRIS and HIV-associated immune pathologies. The clinical manifestations of CNS-IRIS without OI are highly diverse and include encephalitis (65**, 66**,67), demyelinating lesions (65**, 67, 68), and may present as headaches (69, 70), nausea (69), hearing impairment (69), weakness (70, 71), impaired speech (71), disorientation and ataxia (72**) or ischemic events (6). Although the exact forces driving the immune system are not well defined, the immune response may be directed at residual virus in the CNS, persistent release of HIV-Tat protein from HIV infected cells despite control of viral replication or to self-antigens (Figure 2). In one well studied cohort of 10 patients treated with ART that developed subacute encephalopathy, biopsy pathology demonstrated robust CD8+ lymphocyte infiltration both in the parenchyma and perivascular regions (65**). Furthermore, reactive astrocytosis and microglial activation were ubiquitous. Axonal damage and loss of myelin were observed in a subset of patients. When corticosteroids were initiated in these patients 60% showed improvement neurologically and had decreased presence of CNS lymphocytes. The other patients continued to deteriorate with 40% fatality in this cohort (65**). Within this cohort, six patients had increasing viral loads which may indicate that the immune response was targeted at HIV. However, three of the patients developed neurological symptoms after the initiation of ART without an increase in viral load; one at three months, one at nine months and one at two years post-ART-initiation, all coinciding with increasing CD4+ cell counts (65**, 66**). All of these findings are highly suggestive of IRIS. Importantly, of these patients 66% (2/3) improved with corticosteroids and 33% (1/3) died.

Acute versus Chronic IRIS

In addition to suggesting that IRIS may mimic HIV-mediated encephalitis this cohort also supports the concept of acute and chronic IRIS (Figure 3). Two of the three patients developed immune pathology within a year of initiating ART, whereas one patient developed immune pathology two years after initiation of ART (65**, 66**). Case reports of CNS-IRIS in the absence of OI suggest that there can be varying degrees of onset and severity. A case report describes a patient with rapid immune recovery (CD4+ count 133/mm^3 to 1,251/mm^3 in three months) and severe neurological impairment including deafness

that improved with corticosteroid treatment (69). Biopsy showed infiltrating lymphocytes, primarily CD8+ cells, neuronal loss and fibrous astrocytosis. This patient showed substantial neurological improvement and returned to work. In this case, the presence of HIV in the CNS was not examined. In a separate report, a patient developed neurological complications 10 years after initiation of ART. Initially treated with corticosteroids the patient improved and two years later relapsed with ongoing neurological complications. Corticosteroids were again employed with slight improvement. After an additional two year interval modification to ART regime to improving CNS penetration was included as well as an additional corticosteroid intervention. Brain biopsy showed robust CD8+ lymphocytic infiltrates, some CD4+ cells and occasional IL-17+ cells. There were no HIV p24 in the CNS but robust levels of HIV Tat (72**). This patient has a permanent cognitive impairment. Similar cases have been reported. In a cohort of six patients examined for suspected IRIS, one developed neurological complications 10 years after ART initiation with CD8+ parenchymal and perivascular infiltrates and lasting sequelae whereas one patient developed neurological signs five months after ART initiation. Immune restoration was rapid and dramatic and biopsy showed CD8+ infiltrates. The patient improved with CNS penetrating ART (70). Other reports indicate IRIS may occur two years after initiation of ART, with recurrent bouts of resolving neurological complications (68) or as severe neurological manifestations three weeks after ART initiation that improved with corticosteroid use but worsened and caused fatality during corticosteroid taper (71). Together these cases, in conjunction with the previously described cohort, suggest that IRIS may develop in an acute or chronic form (summarized in Table 1). Both forms of IRIS are associated with increasing CD4+ cell counts, and therefore are a reflection of ongoing immune restoration. Immune response in these patients may be targeted against replicating virus in the brain or HIV-Tat protein if viral replication is controlled by ART.

Chronic IRIS and Neurocognitive Impairment

Although ART has reduced the occurrence of HIV-associated dementia (HAD) dramatically (73), HAND persists and even asymptomatic cognitive impairment heralds the risk of further cognitive decline (74*). Interestingly, similar to IRIS, the risk of neurocognitive impairment is also tightly correlated with a lower CD4 nadir (75) suggesting that immune depletion then restoration plays an important role in the development of HAND. It is likely that viral entry into the brain occurs during the time of immune depletion and immune restoration targets the virus or viral products in the brain. Preliminary data from our laboratory suggests that nearly 30-40% of patients with undetectable HIV in the CSF still have detectable HIV-Tat protein, suggesting that it may drive the chronic IRIS and associated neurocognitive impairment. Furthermore, the chronic IRIS form is often associated with recurrent bouts of neurological manifestations that can improve under corticosteroid therapy (68, 72**). This is similar to some autoimmune disorders, such as multiple sclerosis in its relapsing-remitting form (76). The pathobiological mechanisms driving chronic IRIS may be informative for autoimmune diseases in which an underlying pathogen is suspected but not detected.

Approaches to treatment

As discussed above corticosteroids have been often used to treat CNS-IRIS. While short term use of corticosteroids seems safe, long term use has the potential for development to OI and other know sequelae such as bone mineral loss and adrenal suppression. Hence other approaches need to be considered. In patients with viral escape, i.e., who have higher viral loads in the CSF compared to the blood, antiretroviral regimen should be altered to include those that have a higher CNS penetration. In patients who develop autoimmune responses to CNS antigens, therapies that block lymphocyte trafficking into the CNS such as natalizumab may be considered. This is preferable to other drugs that target activated lymphocytes, since natalizumab leaves the peripheral immune system intact. However due to the risk of PML associated with this drug only patients known to be negative for antibodies to JC virus should be treated. Patients with detectable Tat protein in CSF in the absence of detectable HIV should ideally be treated with a Tat antagonist. However in the absence of such a compound, T cell trafficking to the brain should be controlled as mentioned above.

Conclusion

CNS-IRIS and chronic CNS inflammation in HIV infected populations is a serious complication associated with ART. The syndrome has a varied clinical presentation with acute to chronic forms and thus remains under recognized. Treatment strategies may vary depending on the underlying pathophysiological mechanism but patients should be continued on a CNS penetrating ART regimen with aggressive treatment of an underlying opportunistic infection and liberal use of corticosteroids as necessary. Acute forms of CNS-IRIS may be prevented by starting ART early in the course of infection, delaying ART in patients with OI being treated with antimicrobials and avoiding strategies that lead to activation of viral reservoirs.

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Key Points

1. CNS-IRIS in the absence of opportunistic infections may be much more common than originally found and may range from acute fulminant forms to chronic forms that lead to progressive T cell mediated neurodegeneration.
2. In the subacute or chronic forms of CNS-IRIS despite adequate control of HIV replication, there is continued released of HIV-Tat protein which is a potent activator of T cells and results in a T cell mediated encephalitis.
3. In patients with opportunistic infections and CNS-IRIS, antiretrovirals should be delayed by a few weeks if antimicrobials are available to treat the opportunistic infection. However in patients with PML, antiretrovirals should not be delayed even at the risk of developing IRIS.
4. Extreme caution is necessary in the use of therapeutic strategies that are based on reactivation of viral reservoirs, since they may result in IRIS within the brain.

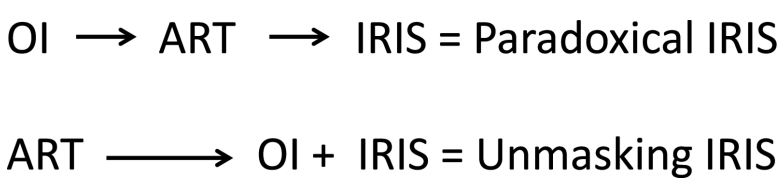

Figure 1.
Paradoxical IRIS is the worsening of a recognized OI after ART initiation whereas Unmasking IRIS is the revealing of an underlying OI after the initiation of ART.

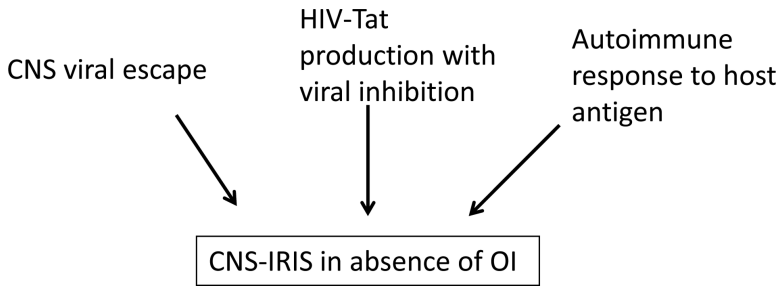

Figure 2.
In the absence of an OI, CNS-IRIS may be driven by multiple antigenic stimuli.

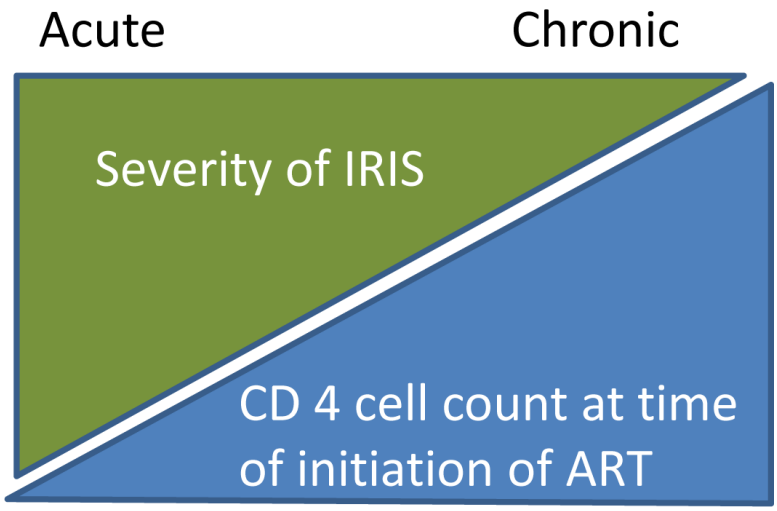

Figure 3.
There is an inverse relationship between the severity of CNS-IRIS and the degree of immune suppression at the time when ART is initiated.

Table 1

Comparison of acute and chronic CNS-IRIS.

	Acute CNS-IRIS	**Chronic CNS-IRIS**
Timing	<1 year after initiation of ART	>1 year – 10 years after initiation of ART
Presentation	Severe clinical signs, eg. Encephalitis with seizures, altered consciousness and focal signs	Moderate to subtle clinical signs that may spontaneously remit; clinical signs may worsen over time; eg. headache, nausea, impaired hearing and vision, weakness, neurocognitive impairment
MRI	May have enhancing lesions or increased water signal	Generalized or subcortical atrophy
Prognosis	Potential for good recovery if intervention is rapid	Permanent impairment from accumulating CNS damage