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Immune Reconstitution Inflammatory Syndrome in HIV Patients Initiated On Highly Active Antiretroviral Therapy

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Abstract
Background: *Immune reconstitution inflammatory syndrome (IRIS) in Human Immunodeficiency virus (HIV) patients receiving highly active antiretroviral therapy (HAART) is on a rise in third world countries. The diagnosis is a dilemma for the treating physician. Here we provide information on the clinical manifestations, outcomes of IRIS and the correlation of time of IRIS with the CD4 count.*
Methods: *A Prospective descriptive study conducted over a period of two years in a tertiary care teaching institute in south India. A total of 516 patients diagnosed with HIV were started on Lamivudine and Nevirapine based regimen of which 40 who developed IRIS were studied. Inferential statistical analysis was applied.*
Results: *The mean time for development of IRIS was 75 days into HAART. Most were in the age group 31-40yr (42.5%) with male preponderance (67.5%). Fever was the most common complaint (67.5%) followed by headache. Haemoglobin at the time of diagnosis of IRIS was usually low.CD4 count at the start of therapy averaged at 125/mm3 and mean increase in CD4 count was 50.3% .Tuberculosis (pulmonary TB) was the most common infection leading to IRIS. Majority (93.75%) of the cases had mild to moderate outcomes.*
Conclusion: *IRIS been firmly established as a significant problem in both high and low income countries. Clinicians when initiating ART should have a high degree of clinical suspicion and individualize therapy according to known treatment options for the specific infectious agent. Early recognition and treatment has drastic impact on the outcome of IRIS.*
Keywords: *antiretroviral therapy, HIV, Immune reconstitution inflammatory syndrome (IRIS), tuberculosis.*

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I. Introduction

Initiating highly active antiretroviral therapy (HAART) to treat Human Immunodeficiency Virus (HIV) infection helps to restore CD4+ cell count and immune function, which is associated with significant reduction in morbidity and mortality. This is due to a rapid phase of restoration of pathogen-specific immunity[1,2].These immunological changes correlate with clinical benefit, reducing the frequency of opportunistic infections and prolonged survival[2]. A subgroup of patients experience clinical deterioration as a direct consequence of rapid and dysregulated restoration of antigen specific immune responses during ART. This is termed as immune reconstitution inflammatory syndrome (IRIS), also known as `immune reconstitution` or `immune restoration disease' [1, 2]. IRIS can be infectious or non infectious. There are two kinds of infectious IRIS – `paradoxical` and `unmasking'. It can result in deterioration of an infective process as in paradoxical IRIS or unmasking of a clinically undetected infection. Incidence, risk factors and time of development of IRIS are variable. There is no specific test at present to diagnose it early [3]. Tuberculosis is the most common cause of IRIS among HIV patients. Less common are varicella zoster, cytomegalo virus, cryptococcus, toxoplasmosis and atypical mycobacterium [3]. With declining costs of antiretroviral drugs and production of generic drugs, tertiary care centres in the developing countries are now able to afford and administer ART to HIV seropositive patients[4].The incidence of immune reconstitution syndrome in such settings will be high[5]. Recognition of IRIS is difficult to the physician especially in resource limited settings.

II. Aims & Objectives

Our objective was to study the various clinical manifestations, risk factors and outcomes of IRIS. We also assessed whether there was any correlation between CD4 counts and various manifestations.

III. Materials And Methods

Study design and setting: - This was a prospective cohort study conducted over a period of 2 years in Government Medical College, Thrissur in the Department of Medicine, speciality departments and ART clinic after obtaining Government Medical College Thrissur Institutional Ethics Committee (IEC) and Institutional Research Board (IRB) approval.Study population and technique – 516 newly diagnosed HIV patients were enrolled in the study and started on HAART. Informed consent was taken from all patients before the start of the study.40patients that developed IRIS were studied .Data was collected according to a set questionnaire by interview and clinical examination. All patients were examined personally by the principal investigator. Patients were subjected to baseline investigations to rule out any pre-existing infections A CD4 count was done before commencing HAART. Clinical features and investigation results were recorded. All patients were started on Lamivudine and Nevirapine based regimen, out of which 81.3% of the cases were in combination with Zidovudine and 18.8% were with Stavudine. All patients were followed up for a period of 6 months after the enrollment of the last subject. In the event a patient developed an infectious or non infectious manifestation a second CD4 count was done. A rise in CD4 count along with a proven manifestation whether infectious or non-infectious was considered as IRIS according to the practical definition by National Aids Control Organisation (NACO) which defines IRIS as an occurrence or manifestations of new Opportunistic Infections(OI) within six weeks to six months after initiating ART with an increase in CD4 count. Once diagnosed as IRIS, the different clinical and lab findings were studied. Risk factors for IRIS were noted. The mean time for development of IRIS in different conditions was studied. Correlation was done with time, CD4 count and different manifestations. Statistical methods and tools: Descriptive analysis was carried out in this study. The data analyzer was blinded.The results were expressed as mean. Significance levels were assessed to 95% confidence intervals. Student `t` test was used for paired comparisons of continuous data and chi square test for categorical data. Statistical software - SPSS 15.0, Strata 8.0, Medcalc 9.0 &Systat 11.0 were used for the analysis of the data. Microsoft word and Excel were used to generate graphs and tables.

IV. Results

1. Age – Most patients in the study belonged to 31-40yr (42.5%) category. Mean age was 39.7yrs (Figure 1). 2. Gender – Most patients who developed IRIS were males (67.5%) 3. Examination findings- Fever was the most common complaint (67.5%) followed by headache (32.5%) and cough (27.5%). Fever was mostly low grade but three cases who were diagnosed with tubercular meningitis had high grade fever. Ten cases had lymphadenitis (6 cervical, 2 axillary, 2 inguinal). Neurological manifestations were seen in seven patients (17.5%) of which three were paraplegic, two hemiplegic, one quadriparetic and one ataxic. Visual loss, loose stools, abdominal pain and skin manifestations were seen in a few. 4. Investigations - Mean haemoglobin (Hb) at IRIS was 10.96gm/dl with 13 (32.5%) patients having Hb less than 10g%. Mean ESR was 88.38mm/1st hr. There were eleven cases with ESR above 100. Nine cases were tubercular and remaining two were cryptococcal meningitis. 5. Time of IRIS - 23 cases (57.5%) developed IRIS in 1- 9weeks. Mean time of development of IRIS was 74 +/-6 days.6. CD4 Count - Initial CD4 count at the start of therapy averaged at 125 and final CD4 count at the time of IRIS was 188. Mean increase in CD4 count was 50.3%. For tuberculosis IRIS, CD4 at the start of therapy was 129.82 and final CD4 count was 190.48. For other diseases, 115.25 was the old and 184.25 was the new CD4. There was no correlation between time of IRIS and CD4 count. IRIS could develop at any percentage increase in CD4 count.7. Diagnosis – Most common cause of IRIS was tuberculosis constituting 70% of the cases. In tuberculosis, lymphadenopathy was the most common manifestation (17.5%) followed by pleural effusion (15%) and meningitis (12.5%). 12 cases were non TB related of which cryptococcal meningitis constituted the next largest group with 7 cases (17.5%), herpes zoster 2 cases, CMV retinitis, isosporiasis and HIV myeloradiculopathy 1 case each. 8. Outcome - One death was reported during the study. The patient had comorbidities like diabetes and bed sores.

TABLE 1.EXAMINATION FINDINGS IN IRIS

Examinations	Number (n=40)	%	95%CI
1.Fever	27	67.5	52.02-79.92
2.Headache	13	32.5	20.08-47.98
3.Cough	11	27.5	16.11-42.83
4.Swollen Lymphnodes)	10	25.0	14.19-40.19
5.Chest pain	9	22.5	12.32-37.50
6.Neurological deficits	7	17.5	8.75-31.95
7.Abdominal Distension	5	12.5	5.46-26.11
8.Cough with expectoration	4	10.0	3.96-23.05
9.Hemoptysis	3	7.5	2.58-19.86

10.Abdominal pain	3	7.5	2.58-19.86
11.Skin manifestations	2	5.0	1.38-16.50
12.Vision loss	1	2.5	0.4-12.88
13.Loose stools	1	2.5	0.4-12.88

Table 2. Mean Time of Development Of Iris

Diagnosis	Number (n=40)	IRIS		
		1-9 weeks (n=23)	10-19 weeks (n=12)	20 & weeks (n=5)
TB manifestation	28	19(82.6%)	6(50.0%)	3(60.0%)
1.lymphadenitis	7	5(21.7%)	2(16.7%)	0(0%)
2.Pleural effusion	6	4(17.4%)	1(8.3%)	1(20.0%)
3.Meningitis	5	3(13.0%)	1(8.3%)	1(20.0%)
4.Disseminated TB	4	2(8.7%)	2(16.7%)	0(0%)
5.Lung Parenchymal TB	2	2(8.7%)	0(0%)	0(0%)
6.Abdomen	1	1(4.3%)	0(0%)	0(0%)
7.Arachnoiditis	1	0(0%)	0(0%)	1(20.0%)
8.Epidural abscess	1	1(4.3%)	0(0%)	0(0%)
9.CNS granuloma	1	1(4.3%)	0(0%)	0(0%)
Other manifestation	12	4(17.4%)	6(50.0%)	2(40.0%)
1.Cryptococcal meningitis	7	2(8.7%)	3(25.0%)	2(40.0%)
2.herpes zoster	2	2(8.7%)	0(0%)	0(0%)
3.CMV retinitis	1	0(0%)	1(8.3%)	0(0%)
4.HIV myeloradiculopathy	1	0(0%)	1(8.3%)	0(0%)
5.Isosporiasis	1	0(0%)	1(8.3%)	0(0%)

Table3. Cd4 Counts In Iris

CD4 count	CD4-Initial		CD4 –Final	
	No	%	No	%
1-50	8	20.0	0	0.0
51-100	9	22.5	6	15.0
101-200	16	40.0	20	50.0
201-300	6	15.0	7	17.5
301-400	1	2.5	7	17.5
Total	40	100.0	40	100.0
Mean ± SD	125.45±77.22		188.60±98.61	
Inference	**CD4 is significantly increased (50.3%) with P<0.001****			

Table 4 Correlation Between Time Of Iris And Cd4 Count.

IRIS (weeks)	Number (n=40)	CD4-Initial	CD4-Final	% Change	P value
1-9 weeks	23	131.78±67.94	198.04±83.12	50.3%	<0.001**
10-19 weeks	12	96.00±85.51	152.83±109.84	59.2%	<0.001**
20 & above	5	167.00±87.47	231.00±131.34	38.3%	<0.001**

Table 5.Common Diagnoses In Iris

Diagnosis	Number n=40 (%)	CD4-Initial	CD4-Final	% Change In CD4
TB manifestation	**28(70.0)**	129.82	190.48	46.73%
1. lymphadenitis	7(17.5)	109.86	189.29	72.30%
2.Pleural effusion	6(15.0)	181.33	246.83	36.12%
3.Meningitis	5(12.5)	122.20	181.20	48.28%
4.Disseminated TB	4(10.0)	53.25	96.25	80.75%
5.Lung parenchymal TB	2(5.0)	190.00	218.00	14.74%
6.Abdomen	1(2.5)	22.00	80.00	263.64%
7.Arachnoiditis	1(2.5)	249.00	286.00	14.86%
8.Epidural abscess	1(2.5)	111.00	131.00	18.02%
9.CNS granuloma	1(2.5)	192.00	303.00	57.81%
Other manifestations	**12(30.0)**	115.25	184.25	59.87%

1.Cryptococcal meningitis	7(17.5)	109.00	171.29	57.15%
2.Herpes zoster	2(5.0)	100.00	191.50	91.50%
3.CMV retinitis	1(2.5)	38.00	56.00	47.37%
4.HIV myeloradiculopathy	1(2.5)	68.00	113.00	66.18%
5.Isosporiasis	1(2.5)	314.00	460.00	46.50%

V. Discussion

The study was carried out in one of the largest ART centres in South India, with highly trained faculty conducting regular monitoring and follow up of HIV patients. We noted a male preponderance (67.5%) to IRIS in our study. These results were similar to other prior studies [5].Whether this could be due to better access to health care systems in India for males or whether IRIS has a gender preponderance need be further evaluated. Most patients in our study were in the age group less than 40yrs which may be attributed to the higher incidence of HIV in the sexually active age group.Fever was the most common complaint followed by headache ough and lymphadenopathy while Walker et al it was fever followed by lymphadenopathy[6]. ESR was high in the present study and it marks the presence of inflammation. Most of the patients with high ESR i.e. >100mm/1st hr (22.5%) had tuberculosis. Cases of cryptococcal meningitis also had high ESR. A high ESR is not diagnostic of tuberculosis nor of cryptococcal meningitis, but the presence of a high ESR should warrant evaluation for the same in clinically suspected IRIS. This finding was consistent with earlier studies by Murdoch et al where they had 34 patients with ESR above 100 and of which 76% had tuberculosis [7]. Majority of the individuals in this study developed IRIS within 9 weeks, the mean time being 75 days which was also consistent with prior studies [7,8]. For tuberculous IRIS the mean time was 12.8 weeks with TB Lymphadenitis, pleural effusion and abdominal tuberculosis occurring between 8-9 weeks whereas Tuberculous CNS involvement in IRIS developed late between 10 to 30weeks. Tuberculosis was the most common cause of IRIS which can probably be attributed to the high incidence of the disease in India[9]. Certain other studies too concluded that tuberculosis was the most common opportunistic infection in IRIS with an incidence of 54%, and tuberculous lymphadenitis being the commonest presentation [7]. CNS tuberculosis in our study manifested between 4 -28 weeks. It has been seen that the early initiation of ART in tuberculous IRIS has a great effect in reducing mortality due to the same[10]. 12 cases were non TB related of which 7 had cryptococcal meningitis, 1 had CMV retinitis and 1 had Herpes zoster. Cryptococcal meningitis IRIS in the present study formed the second largest group with 17.5% of cases. All cases presented with neck stiffness. It occurred as early as 8 weeks to as late as 24 weeks from start of HAART therapy. In contrast with other studies, cryptococcal disease incidence is highly variable[11].Lewis et al.concluded most of the cases (68%) presented as cryptococcal IRIS in his study. Time of onset is anywhere between 7 days to 4 weeks [12].Herpes zoster was the next common cause accounting for 5 % of total and presented with multiple dermatomal blister formation. The initial mean CD4 count at the start of therapy was 100 and at the time of diagnosis of IRIS, the mean count was 191.5 which corroborates with the study by Sharma et al [13].One case of CMV retinitis IRIS was seen in the present study (2.5%). It was a male who developed sudden loss of vision 9 weeks after initiating HAART. CMV infection is shown to occur at low CD4 counts of less than 50/mm3 and cause permanent blindness due to retinitis[6]. The mean CD4 count at the start of therapy averaged 125.45 and final CD4 count at the time of IRIS was 188.6 .Mean increase in CD4 count was 50.3%.The various manifestations also showed an increase in CD4 counts when IRIS set in (Table 3). Thus we conclude that a low CD4 count is an independent risk factor for development of IRIS. Other studies have also concluded similarly [7] .In this study we also found there was no correlation between time of development of IRIS and the percentage change in CD4 count(Table 4). This warrants the treating physician to be more prepared due to the unpredictable onset of IRIS. There was one death in this study. The question whether the death could be attributed to IRIS per say still remains.CD4 count could not be correlated with time of IRIS and death. Comparing other studies, where 68% of the patients had mild outcome [7] Risk factors for developing IRIS in the present study were age less than 40, male patient, low haemoglobin levels and low CD4 at the start of HAART therapy. These findings were consistent with study by French MA et al which concluded that higher baseline CD4 count was protective[14].

VI. Limitations

Study was conducted in a centre were patient follow up was difficult due to multiple reasons like low level of literacy, financial constraints, geographical difficulties. Majority of the patients belonged to low socio economic income class so even some baseline investigations (like viral load testing) were not affordable. The study was not double blinded so probability of bias may be present.

VII. Conclusion

Diagnosis of IRIS by itself is a challenge to the physician due to the varied presentations and aetiologies. A high degree of clinical suspicion is always needed based on the risk factors proposed and awareness needs to be imparted regarding early recognition of IRIS. Underlying opportunistic infections in HIV patients should be actively searched to minimize the development of IRIS, and individualize therapy according to known treatment options for the specific infectious agent related to IRIS. There is a need to develop standardized disease-specific clinical criteria for common underlying infectious disease to identify risk factors for developing IRIS. Early recognition before CD4 counts fall and appropriate treatment drastically influence the outcome of IRIS. Larger studies are required to generate data for our population addressing the prevention and management of IRIS. Hence promote the importance of more research.

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