July 2009

Adult onset Stills disease in a tertiary care hospital of Pakistan.

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Original Article

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Abstract

Objective: To study the clinical characteristics of Stills disease in a tertiary care hospital of Pakistan and compare it with similar published studies.

Materials and Methods: (Retrospective descriptive study) Thirteen patients with Adult onset stills disease were identified by chart review of last ten years from 1995 to 2005 at Aga Khan University Hospital (AKU), a tertiary care private medical university in Karachi Pakistan. Demographic and other specific information was recorded on standardized data sheet and analyzed by SPSS 11.5 software.

Results: Mean age of patients was 26.54±10.34 years, of which 8 (61.5%) were males. The most common presenting features were fever (100%), arthralgias and myalgias (100%) with large joint involvement (91.7%), significant weight loss (30.8%), sore throat (53.8%). None of the patients had skin rashes with fever, chest and abdominal pains. One patient had cervical lymph node swelling and 4 (33.3%) patients had splenomegally. The common laboratory findings were: leukocytosis and anaemia (100%), elevated ESR and C reactive protein (100%). Thrombocytosis (56.2%) and elevated Liver function tests (62%). Seven patients had serum ferritin checked which was in the range of 1872 to 16652 iu/l. None of the patients had positive ANA, Anti-DNA or RA factor. Twelve patients had a chest x-ray done, among them 11 were normal, one had pleural effusion. The clinical course of the patients who were followed for three months, was monocyclic (53.8%), polycyclic (30.8%) and persistent (15.4%).

Conclusion: Clinical characteristics of Stills disease in our country are mostly similar to those seen in other regions, suggesting that same pathogenetic factors may be implicated in patients from different genetic back grounds and geographic locations (JPMA 59:464; 2009).

Introduction

A reterospective descriptive chart review was completed on all patients diagnosed as Adult Onset Stills Disease (ASOD) between January 1995 and January 2005, in a tertiary care hospital.

To diagnose AOSD, 5 or more criteria as described by Yamaguchi[1] were used. These included 2 or more of the major criteria (fever of 39°C or greater lasting for a week or longer, typical rashes, and leukocytosis of 10,000/mm^3 or greater with 80% or more granulocytes), with the rest as minor ones (sore throat, lymphadenopathy, and/or splenomegaly, liver dysfunctions, and negative RF, and negative ANA). Other etiologies like infections, malignancies, and other Rheumatic diseases were excluded by appropriate laboratory tests.

The pattern of the fever was classified as continuous (when there was persistent elevation of the temperature without diurnal variation) or intermittent (when the temperature rose above the normal and returned to baseline each day).

The clinical course of the disease was defined according to Cush et al.[2] The clinical out come of the patients were described in our study as monocyclic (A single episode of the fever and systemic disease followed by complete recovery), polycyclic (2 or more episode of the fever and systemic disease separated by at least two months interval) and chronic articular pattern (patients who had predominatly articular disease with or without systemic disease).

Data was recorded on a standardized data sheet and analysed on SPSS11.0 soft ware. Chi square and fisher exact tests were used to analyse stastical significance among different variables.

Results

During this study period, 13 patients were diagnosed with AOSD, among them there were 8 males (61.5%) and 5 (38.5%) females. Their mean age was 26.54 ± 10.34 years.

All patients had fever of more than two weeks . and all of them were seen by other physicians before the diagnosis was made. Twelve patients had fever greater than 39°C (92.3%). The pattern of the fever varied between continous and intermittent with the intermittent pattern observed among 9 (69.2%) patients and continous among 4 (30.8%). Decreased body weight was observed in 4 (30.8%).

Arthralgias were seen in all patients with

predominant involvement of knees and ankles and lesser involvement of small joints. Arthritis defined as swollen warm and tender joints was encountered in only 2 patients and this was predominantly polyarticular arthritis. Synovial fluid analysis was not obtained in any of the patients. Myalgias were seen in all patients but none had elevation of muscle enzymes. Diffuse erythematous maculopapular rashes involving trunk upper and lower extremities were not observed in any of the patients. Seven (53.8%) patients complained of sore throat. The throat was red but without any exudate. Throat swabs and cultures were negative in all patients. Lymph adenopathy was seen in 1 (7.7%) with involvement of cervical lymph nodes. Hepatosplenomegaly as demonstrated by physical examination and confirmed by ultrasound scan was present in 4 (30.8%) patients.

At presentation anaemia (Hgb <12gm/dl) was observed in 12 (92%) patients and was classified as normochromic normocytic anaemia, with a mean Haemoglobin of 10.63±1.24 gm. Leukocytosis was present in all patients with a mean value of 20.7±4.84/cu mm^3. ESR was elevated in all patents with mean value of 89±29.93 mm/hr. C reactive protein was done in 7 patients and was found elevated in all with a mean value of 14.80±9.87 units.

Abnormal liver function tests were seen in 12 (62.2%) patients with elevated liver enzymes upto 2-3 times of the normal .Lactic dehydrogenase (LDH)was done in 7 patients and was found elevated in all with a mean value of 1314±952.91 iu/l. No patient had a positive test for hepatitis virus serology. Serum liver enzymes returned to normal when disease was under control.

Antinuclear antibody (ANA), and Rheumatoid factor (RF) were negative in all patients . Serum ferritin was done in 7 patients and was significantly elevated in all with a mean value of 6972±5403.89 iu/l. Chest radiographs revealed minimal effusion in one patient. Radiographs of the joints were performed in all patients and revealed only periarticular soft tissue swelling without any erosive changes.

All patients had used NSAIDS before the hospitilisation for arthralgias and myalgias. After the diagnosis was established only one patient was treated with NSAID with good clinical response, 6 were given systemic steroids in a dose of 0.5 -1mg/kg with a dramatic improvement in fever , arthralgias and myalgias, 2 (15.38%) were given combination of steroids and NSAIDS, 4 (30.7%) received disease modifying drugs in addition to steroids and NSAIDS as a steroid sparing agent and to control persistent arthritis.

Mean regular followup duration of our patients was three months with intermittent clinical follow up later on. The clinical course of these 13 patients was monocyclic systemic disease in 7 (53.8%), polycyclic systemic disease in 4 (30.8%), and chronic arthritis in 2 (15.4%). Among the patient with chronic disease one is still in follow up in Rheumatology clinic and her chronic arthritis is well controlled with combination of steroids, and Methotrexate but she still has episodes of fever if the dose of steroids is reduced.

Discussion

Adult onset Stills disease is a multisystemic inflammatory disorder. It is uncommon as observed in many previously published case series,[2-6] but has been recognized as an important cause of the fever of the unknown origin (FUO).[7,8] In a large multicenter prospective study from tertiary care hospitals in Turkey, Stills disease has been identified as the most common non infectious inflammatory disease (NIID) causing FUO in about 13.6% of the patients.[8]

In our series we found 13 patients with AOSD in 10 years period with an approximate a incidence of 1.3 cases/year indicating that this is an uncommon disease in our population. The lower incidence in our case is comparable to some other series. This difference could be due to the fact that our analysis was done in a tertiary care hospital where only selected cases are admitted and majority of our patients are seen by general practitioners and in government hospitals. Interestingly higher incidence of AOSD was obtained from a Canadian series[5] as well as series of the FUO patients from Turkey.[7,8]

Although AOSD is considered as a disease of young adults it can also be seen in geriatric age group, and the sexes are equally affected. The majority of our cases were young adults and more males compared to females were affected. None of our patients were in Geriatric age group in contrast to some series where geriatric population was also affected.[5] Recently a few case reports have been published describing Adult onset Stills disease in elderly individuals.[9]

Most of our patients presented with high spiking fever, arthralgias, myalgias, anaemia leukocytosis, elevated ESR and Hyperferritinemia. The clinical features, laboratory features and out come in our series are compared with some other larger series (Table 1and Table-2). High grade spiking fever, arthralgias, sore throat, myalgias were the predominant clinical features in our case as seen in other series, however in other published series[2-6] in addition to these features skin rashes lymph adenopathy, serositis hepatosplenomegaly and arthritis are the important clinical features. The different clinical features in most series, including ours, were not statistically significant which

Table-1: Comparision of the laboratory findings of AOSD PATIENTS between our study and other reports (Table 2).

Lab findings	Reginato(4) n=23	Cush(2) n=21	Pouchot(5) n=62	Ohta(6) n=34	Worawit (3) n=16	Present study
Hemoglobin<10mg/dl	NA	16(76.2)	42(67.7)	19(64)	8(50)	12(92.)
WBC/mm3						
>10,000	22(90.6)	NA	58(93.5)	30(88.3	15(93.7)	13(100)
10.000-15,000	18(78.3)	15(71.4	50(80)	NA	13(81.3)	NA
Elevated ESR	23(100)	21(100)	51(82.3)	18(89.2)	8(50)	13(100)
Abnormal LFTS	10(43.5)	15(78.9)	47(75.8)	24(80)	12(75)	13(100)
Positive RF	2(8.7)	1(4.8)	4(6.4)	6(17.6)	0	0
Positve ANA	1(4.3)	0	7(11.3)	3(8.8)	1(6.25)	0

( ) = percent. NA: Not available. * = p,.05 **= p, 0.01

Table-2: Comparision of the clinical features of AOSD among different published reports (Table 1).

Clinical features	Reginato (4)	Cush (2)	Pouchot (5)	Ohta (6)	Worawit (3)	Our Study
Sex (Females)	11(47.8)*	13(61.9)	28(45.2)	23(67.6)	13(81.3)	5(38.5)
Age(15-30)	18(78.3)	17(80.9)	50(80.6)	20(62.5)	14(87.5)	13(100)
Arthralgia	23(100)	21(100)	62(100)	34(100)	16(100)	13(100)
Arthritis	22(95.7)	21(100)	58(93,5)	27(90)	13(81.3)	2(15.58)
Fever.>39	23(100)	21(100)	62(100)*	32(94.1)	14(87.5)	13(100)
Weight loss	NA	14(66.7)	41(75.9)	6(50)	11(84.6)	04(30.8)
Skin rashes	22(95.7)*	18(85.7)	54(87.1)	28(82.4)	11(68.7)	0(0)
Sore throat	21(91.3)*	18(85.7)	57(91.9)**	13(46.4)	10(62.5)	7(53.8)
Lymphadenopathy	12(52.2)	19(90)*	46(74.2)	22(64.7)	8(50)	1(7.7)
Hepatomegaly	6(26.1)	08(38.1)	27(43.5)	22(64.	3(18.7)	4(30.8)
Splenomegaly	5(21.8)	11(52.4)*	34(54.8)*	26(76.5)**	3(18.7)	4(30.8)
Pleuritis	7(30.4)	9(42.9)	34(54.8)**	4(11.8)	2(12.5)	1(7.7)
Pericarditis	5(21.8)	7(33.3)	23(37.1)*	5(14.7)	1(6.3)	0(0)
Myalgias	8(34.8)	16(76.2)	52(83.9)	NA	16(100)	13(100)

() = Percent. * = p<.05 ** = p < .0.01. Chi -square or Fischer exact test was used for categorical variables).

suggests that same pathogenetic factors may be involved in the causation of the disease.

The differences in clinical manifestations are difficult to explain except that evanescent rash may be difficult to detect on the pigmented skin of our patients. The lower incidence of arthritis in our series is surprising and the only explanation could be that almost all of these patients were treated with NSAIDS, before hospitilisation, and that could mask findings of inflammatory arthritis.

Involvement of the Ocular, CNS, and cranial nerves has rarely been reported in AOSD series,[5,6] we report no such association.

We found no significantly different changes in laboratory findings, including complete blood counts, ESR, Liver dysfunction, serum RF, and ANA when compared with other series (Table 2). Mild to moderate Transaminase elevation were observed in most of our patients however none of them progressed to severe liver failure as reported in other series.[6] It is suggested that elevated Transaminase level is not a contraindication to the use of NSAID in this patients and even Transaminase level would improve with the induction of remission with NSAIDS.[7] Interestingly a case of Fulminant hepatic failure in a patient with newly diagnosed Stills disease have been recently reported and it is concluded that Stills disease should be considered in the differential diagnosis of acute hepatic failure as early diagnosis and treatment with steroids will improve the outcome.[10]

The clinical out come in our series was comparable to other series in that the systemic disease course both monocyclic and polycyclic was more common than Chronic articular disease.[3-6] In a recent series from Kuwait,[11] self-limited, intermittent, and chronic disease course was seen in 14.3, 57.1, and 28.6% of patients, respectively. The outcome was good in about 89% of patients, with no mortality.

We don't have any data about the course of AOSD in our patients during pregnancy however in other series[2] no disease flare up was noticed during pregnancy.

Traditionally NSAIDS have been recommended as the initial mode of treatment in AOSD but they have been effective in only 20-25% of the cases.[3,4] Only 1 of 13 patients in our study responded well to NSAIDS and

remaining required steroids which majority of them were able to taper at least in short out patient follow up. This finding is consistent with others in that corticosteroids were effective in controlling systemic symptoms.[3,4] Disease modifying antirheumatic drugs (DMARDS) were used in few of our patients but they have been recommended in addition to steroids to control systemic and chronic articular disease.[12] Biologic agents have been used recently for resistant cases.[13]

The assessment of the disease activity in AOSD is difficult. Serum ferritin in AOSD is of particular interest and it has been proposed as a marker of disease activity. A very high level is observed in patients with active AOSD and the level correlates with the disease activity.[11,14] Serum ferritin was elevated in majority of our patients, however whether levels correlated with disease activity in our series is difficult to detect because of the lack of follow up results in our series. The precise mechanism leading to elevated serum ferritin in our series is unclear.

Conclusion

AOSD in our population has nonspecific clinical features and mimics bacterial infections such as Mycobacterial infections, Pharyngitis, Endocarditis and a high clinical suspicition is required to diagnose this relatively rare but important entity before prescribing unnecessary antiobiotics and antituberculous treatment. There may be interethinic differences in the clinical manifestations and the disease outcomes. Large prospective studies are needed to test this hypothesis.

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