CASE REPORT

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Spondyloarthropathy in Three Generations: Link with Specific HLA Alleles

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Abstract

Spondyloarthropathy (SpA) is a group of rheumatological disorders which may be occasionally clustered in families. There is very little data on familial SpA from India. We here report the case of an Eastern Indian family where SpA was present in three successive generations. The age of onset of the symptoms decreased in successive generations. Only male family members were affected. The affected family members were positive for HLA-B27. Two of the affected members were positive for HLA-DR11 and HLA-DRB3 simultaneously. Genetic associations of familial SpA have also been discussed at length.

Key words: Familial, spondyloarthropathy, HLA-DR.

Introduction

Spondyloarthropathy (SpA) is a group of disorders with the predominant feature of enthesitis and sacroiliitis, along with various extra-articular manifestations[1]. Usually this is a sporadic rheumatological disorder but in some cases, the disease may be clustered in families[2]. It has been found that the familial clustering of SpA may be related to certain genetic factors[2].

Familiality of SpA has been reported from different parts of the world, but there are almost no case studies from India[3]. Risk modelling for SpA done elsewhere has shown definite high risks in near relatives[3]. Hence, familial clustering of SpA needs to be studied in order to understand the risks of recurrence. We report a family of three generations with SpA from Eastern India.

The cases

A 41-year-old male patient came to the medical OPD with the chief complaint of progressive low back pain and stiffness of the back for the last ten years. There was no history of pain in any other joint and no history of red eyes, skin rash or blood in stool. There was significant early morning stiffness and the patient was forced to change his profession as a vegetable seller due to these symptoms. On examination, there was forward bending posture with restriction of rotation of the spine. Bilateral sacroiliac joints were tender. Schober's test was positive. Laboratory tests revealed high ESR (90 mm in the 1st hour) and CRP (48 mg/l). The patient underwent MRI scan of the pelvis with STIR imaging which showed (Fig. 1) bilateral active sacroiliitis.

Family history of the patient revealed that his two other brothers and one of his sons was also suffering from similar complaints. For the brothers, the age of onset of the symptoms was around 20 - 22 years. Both of them had severe stiff back and one of them was home-bound. The patient's son, aged 15 years, had moderate low back pain. Onset of symptoms was at the age of 12 years. The patient's father, aged 72 years, had some stiff back for the last few years, which was attributed to old age. The father had no limitation of activity.

All of the affected family members were summoned and examined. The two affected brothers had some limitation of spine movement in all directions. No peripheral joint was involved. The young 15-year-old son of the patient had tender sacroiliac joints bilaterally but no stiffness of the spine. There was another 12-year-old son who complained of occasional low back pain. But local tenderness or stiffness were absent. None of the family members had any history suggestive of uveitis, inflammatory bowel disease or psoriasis.

All the affected family members, including the father of

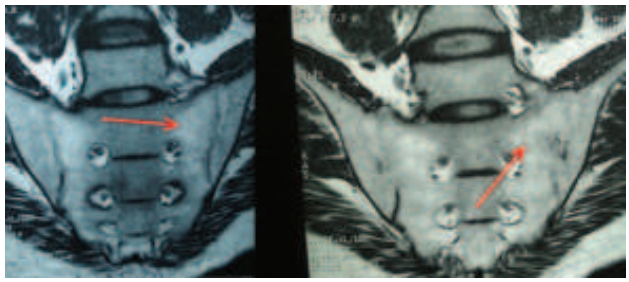

Fig. 1: *MRI of SI joints of the index case (41-year-male) showing bilateral sacroiliitis (red arrows).*

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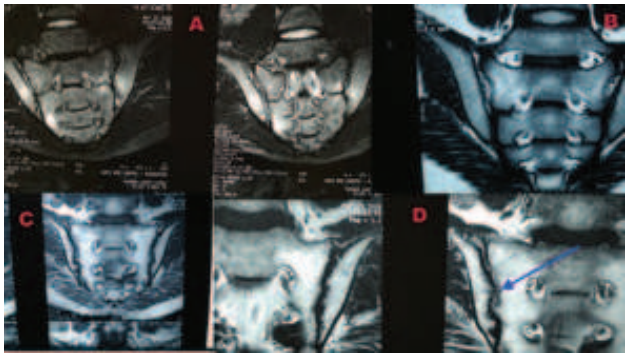

Fig. 2: *MRI scan of pelvis of: A: elder son (15-year-old) showing active sacroiliitis in STIR image; B: younger son (12-year-old) showing early sacroiliitis; C and D: grandfather (72-year-old) showing some bone marrow oedema with partial sclerosis of SI joints (blue arrow).*

the index case, underwent MRI examination of the pelvis. It revealed (Fig. 2) active sacroiliitis in the two young sons and partially sclerosed SI joints with some foci of bone marrow oedema in the grandfather. Some degree of sclerosis of SI joints was also found in the brothers. The partial pedigree chart of the family is shown in Fig. 3.

Genetic study was done in the index case. He was found to be HLA B27 positive. Also, HLA DR DNA analysis (by SSP method) showed DR11 and DR12 to be positive. He was also positive for HLA-DRB3. HLA-B27 was also found to be positive in the two young sons and the affected brothers. One of the affected brothers also underwent genetic study for HLA-DR. It was seen that he was HLA-DR 11 and 15 positive. Also, he was HLA-DRB3 and DRB5 positive. Thus, besides HLA-B27, the other common genetic associations were for HLA-DR11 and DRB3.

The index case was treated with infliximab with marked reduction in the pain. But the stiffness in spine remained. The two brothers were deemed to have burnt out disease and hence, biological therapy was not attempted. They were referred for physiotherapy and rehabilitation. The two young sons were started on DMARDs with good improvement in the pain on follow-up.

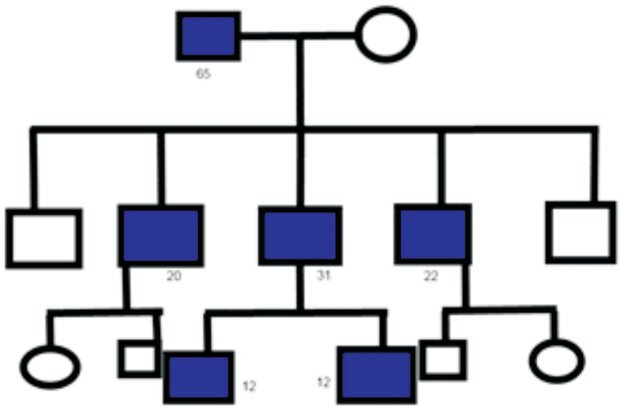

Fig. 3: *Partial pedigree chart of the family (blue filled shapes: affected members; number beside shapes indicate age of onset).*

Discussion

SpA group of disorders may be familial in some cases. The sibling recurrence risk ratio is 82 and the disease is highly concordant among twins[4]. The prevalence of the disease is more among the Caucasian population and familial SpA cases are also reported predominantly in that population[4]. For a European population, the recurrence risk of SpA in 1st degree relatives has been found to be around 8% and for 2nd degree relatives, it is around 1%[5]. There are comparatively much fewer studies from Asia in this regard. One Chinese study reported a recurrence rate of around 4% for 1st degree relatives and 0.8% for 2nd degree relatives[5]. English literature search did not reveal any specific report of familial SpA from India. Hence, the pattern of familial concurrence of this disease in the Indian population is not documented till now. In our family of SpA, out of 8 first degree relatives of the index case, 5 (62.5%) were affected. But only one case series cannot give an idea of the average recurrence rate.

Studies have shown that the familial concurrence of SpA is linked to genetic predisposition[2]. HLA-B27 is the strongest genetic link with SpA. But only HLA-B27 is not enough to explain all the genetic influence[2]. There are other genetic influences, both HLA linked and outside the HLA region, which may be a factor in the etiology of SpA[2]. In a report from the USA, in a family where SpA was transmitted in an autosomal dominant fashion, HLA-B27 was found to be negative[6]. In our series, the affected family members were positive for HLA-B27. However, HLA-B27 is not an essential component of familial SpA, as the aforementioned family from USA demonstrated[6]. Thus, in similar familial cases of SpA, where HLA-B27 is negative, other genetic studies should also be done.

HLA-B27 is a class I MHC gene. But class II genes have also been implicated in the disease. In a study of French families with SpA, HLA-DR4 and HLA-DR13 have been found to be linked with SpA[2]. But the authors of that study stated that the study was underpowered to detect any definite genetic linkage[2]. In another study from the USA, genetic linkage was also found in many non-MHC regions in SpA cases[4]. These other candidate genes include genes for interleukins, ERAP, RUNX or TIMP[5].

Since SpA is a heterogeneous disease, the genetic associations may vary with phenotypic varieties[4]. Most of the studies on genetic linkage has been done with spondylitis or sacroiliitis as the fixed phenotypic variant[4]. In

our case series also, spondylitis and sacroiliitis were the sole phenotypic manifestations.

HLA-DR11 and 12 are variants of the HLA-DRB1 locus. HLA-DRB1 has been found to be linked to SpA[7]. However, different subtypes of that locus have been linked to SpA in different studies. For example, a study in a Mexican ethnic group found HLA-DR8 to be associated with SpA[7]. In other countries, HLA-DR4 or 7 or similar other haplotypes have been linked to the disease[8]. In some cases, a particular HLA allele may not be directly linked to occurrence of the disease, but rather may modify phenotypic expressions like age of onset[8]. For example, HLA-DR7 is linked with younger age of onset[8].

Usually, there is linkage between HLA-B27 and HLA-DRB1[8]. In other words, B27-DRB1 combination confers increased susceptibility to the disease than only HLA-B27 alone[8]. In our case too, the index case was HLA-B27 and HLA-DRB1 positive. But in some other studies, the effect of HLA-DRB1 on SpA has been found to be independent of HLA-B27[9].

In our index case, the patient was HLA-DR11 and 12 positive. His brother was also HLA-DR11 positive. HLA-DR12 is usually negatively associated with SpA[2]. The association of HLA-DR11 with SpA is not well documented. In a study from South India, HLA-DRB1*11 was found to be associated with SpA, but the statistical significance of that association was lost after Yates correction[10]. Thus, the true linkage of HLA-DR11 and 12 in the Indian patients with SpA needs more research.

HLA-DRB3 is linked with DRB1 locus in many people[11]. Especially, DR12 variant is often found to be co-expressed with DRB3[11]. Our index case was also dual positive for DR12 and DRB3. His brother was also positive for HLA-DRB3. But whether DRB3 locus is separately related SpA is not known till now.

The role of HLA-DRB1 gene in the pathogenesis of SpA and similar disorders is far from clear[12]. Moreover, studies have shown that, unlike HLA-B27, the susceptibility for different HLA-DRB1 haplotypes may vary with the population group and ethnicity[12]. Thus, the true significance of HLA-DRB1 in SpA in Indian patients, especially the familial forms, is still a matter of speculation.

A study from Korea found that familial SpA cases had significantly lower frequency of peripheral arthritis[13]. In our case series also, none of the family members had any current of past evidence of peripheral arthritis. Usually, in cases of familial SpA, female gender is more affected[14]. But in our case study, all the affected family members were male.

Thus, SpA is a heterogeneous disease with various possible genetic linkages and phenotypic expressions; thus comparison of familial and sporadic cases may help in elucidating the phenotypic and genotypic spectrum of the disorder.

Conclusion

Spondyloarthropathy is a disease with strong genetic association. Local, population-wise genetic susceptibility patterns must be analysed. Familial SpA cases offer a unique opportunity to study such patterns.

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