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ORIGINAL RESEARCH

A case-control study of Apolipoprotein E Gene amongpsoriasis patients

Farhat Fatma[1], Dr. Jaya Jain[2], Dr. Ashutosh Jain[3], Dr. Anshuman Rai[4], Dr. M S Chandel[5]

[1]Department of Biochemistry, Index Medical College, Hospital and Research Centre, Indore, Madhya Pradesh, India
[2]Assistant Professor, Department of Biochemistry, IMCHRC, Indore, Madhya Pradesh, India
[3]Tutor, Department of Physiology, IMCHRC, Indore, Madhya Pradesh, India
[4]Associate Professor, Department of Skin & VD, GMC, Azamgarh, Uttar Pradesh, India
[5]Deputy Registrar, Academics, Malwanchal University

Correspondence:
Dr. Jaya Jain
Assistant Professor, Department of Biochemistry, IMCHRC, Indore, Madhya Pradesh, India

ABSTRACT

Introduction: Psoriasis is a chronic skin disease of unclear aetiology and pathogenesis which is characterized by an inflammatory infiltration in dermis and epidermis, proliferation of epidermal cells – keratinocytes which clinically manifests with the formation of erythemato-squamose papules, and is often accompanied by the engagement of joints and nails in the process of inflammation.

Materials and Methods: This is a case-control study conducted at Department of Biochemistry, Central Research Lab and Central Clinical Lab of GMC Azamgarh. The subjects will be selected as per the inclusion/ exclusion criteria. A detailed clinical history including age, sex, and occupation will be collected from the patients after obtaining written and informed consent. For ApoE: Genomic Dna is extracted from blood using QIAamp DNA minikit. The genotypes of the APOE polymorphisms is determine by using APOE strip assay kit based on polymerase chain reaction and reverse-hybridization technique.

Result: A total of 380 patients who fulfilled the selection criteria during the study were enrolled, they were divided into two groups case and control each group consist of 190 patients. Maximum number of (41.5%) patients are seen during <1 years of duration of psoriasis followed by 1-2 years are 27.8%, 2-3 years are 22.1% and least are 4-5 years are 1.5%. Most of the patients has plaque type of psoriasis are 88.4% followed by Guttate 8.9% and few are Pustular and Exfoliative 1.5% and 1.0% respectively. Severity of psoriasis is mild 17.8%, moderate 48.4% and severe 33.6%. Apolipoprotein E alleles in cases areε3 83.1% followed by ε4 12.1% and ε2 4.7%. On the other hand, in control group ε3 94.2% and ε4 10%.

Conclusion: Apolipoprotein E may be used as a marker to predict those patients with psoriasis who are at risk of dyslipidemia and probably CVD. Based on the results of our study, we recommend regular monitoring of patients with psoriasis for the presence of comorbidities which have a definite adverse effect on both psoriasis and the CVS.

Keywords: Psoriasis, Apolipoprotein E, Alleles, Plaque.

INTRODUCTION

Psoriasis is a chronic skin disease of unclear aetiology and pathogenesis which is characterized by an inflammatory infiltration in dermis and epidermis, proliferation of

epidermal cells – keratinocytes which clinically manifests with the formation of erythemato-squamose papules, and is often accompanied by the engagement of joints and nails in the process of inflammation. [1] Since its pathology fits the definition of "a clinical syndrome caused by activation of T cells and B cells, or both, in the absence of an ongoing infection or other discernible causes" psoriasis is ranked among autoimmune diseases. [2] A variety of studies suggested that intra-lesional activated T cells produce cytokines that trigger basal stem cell keratinocytes to proliferate and perpetuate the disease. [3]

Prevalence of psoriasis worldwide in adults, the incidence of psoriasis varied from 30.3 per 100 000 person years (95% confidence interval 26.6 to 34.1) in Taiwan to 321.0 per 100 000 person years in Italy.[4] The prevalence of psoriasis varied from 0.14% (95% uncertainty interval 0.05% to 0.40%) in east Asia to 1.99% (0.64% to 6.60%) in Australasia. The prevalence of psoriasis was also high in western Europe (1.92%, 1.07% to 3.46%), central Europe (1.83%, 0.62% to 5.32%), North America (1.50%, 0.63% to 3.60%), and high income southern Latin America (1.10%, 0.36% to 2.96%).[5]

However, the countries with the highest number of adults affected were the US (3.4 million, 95% uncertainty interval 1.5 to 7.7 million), India (2.9 million, 0.8 to 10.0 million), China (2.3 million, 0.9 to 6.1 million), Germany (1.5 million, 0.8 to 2.9 million), Brazil (1.2 million, 0.3 to 4.8 million), France (1.0 million, 0.5 to 2.1 million), and the UK (1.0 million, 0.5 to 1.9). [6]

The etiology of psoriasis remains unclear, although there is evidence for genetic predisposition. The role of the immune system in psoriasis causation is also a major topic of research. [7] Although there is a suggestion that psoriasis could be an autoimmune disease, no autoantigen that could be responsible has been defined yet. Psoriasis can also be provoked by external and internal triggers, including mild trauma, sunburn, infections, systemic drugs and stress. [8]

A majority of those who suffer from psoriasis have a mild disease activity, but approximately 25 percent have been estimated to suffer from moderate to severe psoriasis, and may therefore need conventional systemic treatment to control the disease. Moderate to severe psoriasis is also associated with Crohn's disease, cardiovascular disease, depression and an increased risk of death. [9]

Apolipoprotein E (apoE) is a plasma protein with known functions in plasma lipoprotein metabolism and in lipid transport within tissues. APOE gene is located on chromosome 19 and has three polymorphic variants in human designated as $\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$. These variants differ from one another by the presence of either C or T nucleotide at codons 112 and 158. These three alleles encode different APOE isoforms which vary significantly in structure and function including receptor binding capacity and lipid metabolism. [10]

MATERIALS AND METHODS

This is acase-control study conducted at Department of Biochemistry, Central Research Lab and Central Clinical Lab of GMC Azamgarh.

The subjects will be selected as per the inclusion/ exclusion criteria. A detailed clinical history including age, sex, and occupation will be collected from the patients after obtaining written and informed consent.

SELECTION OF CASES

INCLUSION CRITERIA

1- Psoriasis patients of age group of 18-60years.
2- All patients must be diagnosed for Psoriasis.
3- Subject who will sign the consent form.

EXCLUSION CRITERIA

1- History of Diabetes mellitus and other endocrine Disorders
2- History of Hypertension, Renal disorders, Coronary artery disease.
They are divided into 2 group Case: Psoriasis patients and Control: Apparently Healthy Individuals

SELECTION OF CONTROL

Apparently healthy individuals will be taken as control (age-group: 18-60 years).
Excluded if they had any history of autoimmune disorders.

COLLECTION OF SAMPLES

- 6 ml of Blood sample will collect by venepuncture under aseptic precautions after an overnight fast or 12 hours of fasting.
- Centrifuge at 2000 r.p.m. for 5 min (for serum).
- Then the serum so obtained will be analyzed further.
- 2ml blood will transferred to EDTA for genotyping (apolipoproteinE)
- 2ml of blood will be transferred to plain vial for the estimation of Lipid Profile.
- 2ml of blood will be transferred to a fluoride vial for the estimation of Blood Sugar Levels.

LABORATORY INVESTIGATION

1. For ApoE

- Genomic Dna is extracted from blood using QIAamp DNA minikit.
- The genotypes of the APOE polymorphisms is determine by using APOE strip assay kit based on polymerase chain reaction and reverse-hybridization technique.

STATISTICAL ANALYSIS

Statistical analysis will be conducted by using SPSS version 20.0 (Chicago, US). Mean ± SD (Standard Deviation) of all quantitative clinical parameters will be calculated in patients of psoriasis and healthy controls. Appropriate statistical test will be used to calculate significance (p value) in between the groups. Correlation will be determined by using Pearsons correlation coefficient. The differences in genotype and allele frequencies between patients and controls analyze by fischer's exact test using SPSS software. $p<0.05$ value will be considered statistically significant.

RESULT

A total of 380 patients who fulfilled the selection criteria during the study were enrolled, they were divided into two groups case and control each group consist of 190 patients. The data were analysed and the final observations were tabulated as below.

Table 1: Distribution of the number of subjects according to age group

Age group	Cases		Control	
	Number	Percentage	Number	Percentage
18-30 years	89	46.8	93	48.9
31-50 years	62	32.6	66	34.7
51-60 years	39	20.5	31	16.3
Total	190	100	190	100

In this study, in case group the maximum number of patients were in the age group of 18-30 years which were 46.8% (n =89) of total followed by age group 31–50 years having 32.6% (n

= 62) and 39 (20.5%) were 51-60 years. In control group the maximum number of patients were in the age group of 18-30 years which were 48.9% (n =93) of total followed by age group 31–50 years having 34.7% (n = 66) and 31 (16.3%) were 51-60 years in table 1.

Table 2: Distribution of Gender

Gender	Cases		Control	
	Number	Percentage	Number	Percentage
Male	120	63.1	103	54.3
Female	70	36.8	87	45.7
Total	190	100	190	100

In table 2, of the 190 samples in case group, 120 were males and 70 females, which correspond to 63.1% of male and the rest female. Of the 190 samples in control group, 103 were males and 87 females, which correspond to 54.3% of male and the rest female.

Table-3: Distribution of Height, Body weight and BMI

	Cases (Mean±SD)	Control (Mean±SD)	p-value*
Height (cm)	162.53±13.6	159.65±13.8	0.74
BW(kg)	65.54±6.6	63.65±6.7	0.64
BMI (kg/m^2)	24.80±3.2	25.0±3.7	0.72

*p-values represent the difference between two groups

Ofthe70,meanheight of participants in Case group was162.53±13.6 years and in Control Group was159.65±13.8 years. Mean bodyweight of Case Group were 65.54±6.6 kg and Control Group63.65±6.7 kg, when calculate the mean BMI of Case Group were 24.80±3.2 kg/m^2 and Control Group were 25.0±3.7 kg/m^2 in table 3.

Table 4: Duration of Psoriasis

Duration(Year)	Number	Percentage
<1	79	41.5
1-2	53	27.8
2-3	42	22.1
3-4	13	6.8
4-5	3	1.5
Total	190	100

In table 4, maximum number of (41.5%) patients are seen during <1 years of duration of psoriasis followed by 1-2 years are 27.8%, 2-3 years are 22.1% and least are 4-5 years are 1.5%.

Table 5: Type of Psoriasis

Type of Psoriasis	Number	Percentage
Guttate	17	8.9
Plaque	168	88.4
Pustular	3	1.5
Exfoliative	2	1.0
Total	190	100

In table 5, most of the patients has plaque type of psoriasis are 88.4% followed by Guttate 8.9% and few are Pustular and Exfoliative 1.5% and 1.0% respectively.

Table 6: Severity of psoriasis

Severity of Psoriasis	Number	Percentage
Mild	34	17.8
Moderate	92	48.4
Severe	64	33.6
Total	190	100

In table 6, severity of psoriasis is mild 17.8%, moderate 48.4% and severe 33.6%.

Table 7: Apolipoprotein E alleles frequencies in case and control group.

Allele	Cases		Control		p-value
	Number	Percentage	Number	Percentage	
ε2	9	4.7	0	0	-
ε3	158	83.1	179	94.2	<0.0001
ε4	23	12.1	11	10	<0.0001
Total	190	100	190	100	-

In table 7, Apolipoprotein E alleles in cases areε3 83.1% followed by ε4 12.1% and ε2 4.7%. On the other hand, in control group ε3 94.2% and ε4 10%.

Table8: Apolipoprotein E genotypes frequencies in case and control group

Genotype	Cases		Control		p-value
	Number	Percentage	Number	Percentage	
ε2/ε2	0	0	0	0	-
ε2/ε4	0	0	0	0	-
ε3/ε2	9	9.4	0	0	-
ε3/ε3	63	66.3	82	86.3	<0.0001
ε3/ε4	23	24.2	13	13.6	<0.0001
ε4/ε4	0	0	0	0	-
Total	95	100	95	100	

DISCUSSION

Psoriasis is a chronic immune-mediated inflammatory disease, characterized by keratinocyte proliferation, that is characterized by well-defined red plaques with silvery-white scales, which can involve any region of the skin (and other components of the integumentary system, including the nails), but is usually located on the elbows, knees, scalp and presacral region.[11] With a prevalence of 0.1-3% in various populations, psoriasis can start at any age (but often presents between 15 and 30 years) and appears to be equally common in both male and female patients. [12] As regards the pathogenesis of psoriasis, it involves a genetic component (association with HLA-Cw6 and a positive family history) and an immune dysfunction, with the added contribution of numerous environmental factors (including infections, trauma, medications and psychological stress). [13] The immune response is characterized by the proliferation of T helper (Th)1, Th17 and Th22 cells, which results in the production of proinflammatory mediators, including IFN-γ, IL-6, IL-22 and TNF-α, which serve an important role in maintaining chronic inflammation in psoriasis. [14]

Apolipoproteins are the protein part of lipoproteins, and their composition is specific for each lipoprotein. They have a different molecular structure, amino acid composition, and antiatherosclerotic properties. In psoriatic patients, different results concerning apolipoproteins apoA1, apoB, and apoE were presented. [15] Apolipoprotein A1 has been immunocytochemically detected at the psoriatic skin dermoepidermal junction, vascular

walls, and the perivascular region of papillary dermis. Apolipoprotein B100 and apolipoprotein E were observed intracellularly both in normal epidermis and psoriatic epidermis, and they were also detected in parakeratotic regions in the horny layer. [16]
ApoA1 plays the main part in the reverse cholesterol transport from the peripheral cells to the liver. Its decreased level has an influence on the higher risk of atherosclerosis development. [17] ApoA2 stabilizes the HDL structure and is considered as the lecithin: cholesterol acetyltransferase (LCAT) inhibitor. Its role concerning atherosclerosis is controversial, because it was shown that apoA1 impaired the inflow of cholesterol from adipocytes to the extracellular space. [18] Elevated levels of apolipoproteins A1 and A2 accompany the intake of alcohol. The level of apoA1 increases also in familiar hyperproteinemia, in pregnancy, during estrogen therapy, and during physical exercise. [19]
Elevated levels of apolipoprotein B are associated with the increased risk of atherosclerosis, due to its role in the cholesterol accumulation in the endothelium, which initiates the atheromatous process. Apo B elevated levels are observed in the hyperlipidemia type IIa, IIb, IV, and V, in nephritic syndrome, pregnancy, familiar hyperapo--lipoproteinemia, biliary obstruction, smokers, and dialyzed patients on treatment with diuretics -blockers, cyclosporine, or glucocorticoids. [20]
Apolipoprotein C3 (apoC3) is suggested to inhibit lipoprotein lipase and hepatic triglyceride lipase, enzymes responsible for the clearance of triglyceride rich particles from the plasma. Furthermore, apoC3 was shown to inhibit the hepatic uptake of triglyceride rich particle. [21] Apo C3 also appears to interfere with HDL receptor-mediated uptake of lipoproteins. It is known that an increase in apoC3 levels induces the development of hypertriglyceridemia. [22]
In most studies, elevated levels of apoA1, apoB, apoC3, and apoE were detected in the serum of psoriatic patients compared to the healthy control group. However, there are also contrary results showing decreased levels of apolipoproteins. [23] Many authors did not show any differences in apoA1, apoA2, and apoB levels between psoriatic patients and the control group. [24] It was also reported that apoA1 sequestration in the inflamed tissues might lead to reduced HDL-C serum levels and thus increase the risk of cardiovascular disease in psoriatic patients. [25]
Apolipoprotein E (ApoE) is a glycoprotein involved in the regulation of triglycerides and low-density lipoprotein (LDL) levels. ApoE can modulate mitogen-activated T-lymphocyte proliferation in vitro and provides protection against some infections. [25] The role of the apoE gene in psoriasis was suggested, because in psoriatic skin there is the downregulation of ApoE expression and the normalization of ApoE levels precedes clinical improvement. [26] Furthermore, in a Japanese population the epsilon 2 allele was found to be significantly more frequent in psoriatic patients than in controls, suggesting that there may be a relationship between these particular alleles and development of psoriasis. [27] It is believed that the epsilon 4 allele could be a risk factor for developing a severe form of psoriasis. [28]

CONCLUSION

Apolipoprotein E may be used as a marker to predict those patients with psoriasis who are at risk of dyslipidemia and probably CVD.Based on the results of our study, we recommend regular monitoring of patients with psoriasis for the presence of comorbidities which have a definite adverse effect on both psoriasis and the CVS. Early detection and control of these risk factors is imperative to reduce the morbidity and mortality associated with these conditions, and to provide a better quality of life to these patients.

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