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PREVALENCE OF N34S MUTATION OF THE SPINK1 GENE IN ALCOHOLIC CHRONIC PANCREATITIS

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ABSTRACT To detect the prevalence of N34S mutation of the SPINK1 gene in alcoholic chronic pancreatitis patients and gene differs between patients with alcoholic chronic pancreatitis. Total of 50 Alcoholic chronic pancreatitis patients was admitted In Department of Gastroenterology, Osmania General Hospital. In the present study it was observed that 46 % patients were in the age group of 41-50 years, age range was between 33 years to 67 yrs. Further more studies are needed to be done to substantiate the results and to clarify the influence of SPINK1 N34S on the pathogenesis and clinical course of alcoholic chronic pancreatitis. The role of genetics in Alcoholic Chronic Pancreatitis and genotype phenotype correlations. Also, it may be useful to do functional studies of SPINK1 mutation in cell cultures to understand the pathophysiology of disease status more completely.

KEYWORDS : N34S Mutation, SPINK1 Alcoholic, Chronic Pancreatitis

INTRODUCTION

Chronic pancreatitis is a progressive inflammatory disease of the pancreas characterized by chronic inflammation and progressive fibrosis with loss of both 19 exocrine and/or endocrine function. Irrespective of the etiology, the clinical pattern of chronic pancreatitis is characterized by an early stage with recurrent episodes of acute pancreatitis followed by a late stage with pancreatic calcifications, pancreatic insufficiency, and diabetes mellitus in the majority of patients. It is a significant health problem worldwide and is associated with considerable morbidity. Prevalence & etiology of CP varies widely in different geographic locations. Alcohol is the most frequent cause of CP worldwide[1].

Despite Alcohol being a risk factor for most cases of chronic pancreatitis, Alcohol alone does not directly cause pancreatitis, and the pathophysiological mechanisms responsible for alcoholic CP remain unclear; in fact, only a small proportion of chronic alcoholics (5-10%) have the disease.[2,3]

The prevalence of CP was reported to be around 10/100 000 in earlier reports. Compared with 10-15 per 100,000 prevalence in Western countries, the prevalence of CP is higher in India and some of the other Asian countries[4]

However, more recent studies have shown a higher prevalence of CP in different countries: 13.52/100 000 in China, 26.4/100 000 in France, 41.8/100 000 in USA, and 45.4/100 000 population in Japan. CP is widely prevalent in Asia, the highest prevalence has been reported to be 125/100 000 population from India[5]

AIMS AND OBJECTIVES

1. To detect the prevalence of N34S mutation of the SPINK1 gene in alcoholic chronic pancreatitis patients.
2. To establish whether the frequency of the N34S mutation of the SPINK1 gene differs between patients with alcoholic chronic pancreatitis, Alcoholics without pancreatitis and healthy controls

METHODOLOGY

Total of 50 Alcoholic chronic pancreatitis patients who either attended outpatient or admitted duration from November 2016 to December 2018, Osmania General Hospital and a total of 25 Alcoholics and 25 Healthy controls who attended the outpatient department.

Exclusion criteria

Patients who have the disease but do not have a personal history of alcohol abuse

Inclusion criteria: Age >18 years

Diagnosis of chronic pancreatitis was established based on routine criteria: history of recurrent episodes of acute pancreatitis and abnormalities detected by imaging studies (ultrasonography, abdominal computed tomography, endoscopic retrograde cholangiopancreatography) such as calcifications, parenchymal fibrosis, calcified deposits in the pancreatic ducts, or widened/irregular ducts.

Alcoholic etiology was determined on the basis of medical history, i.e., consumption of more than 80 g of pure ethanol/day (men) and more than 40 g of pure ethanol/day (women) over at least 5 years.

Healthy controls

This group included healthy volunteers with no history of alcohol intake.

RESULTS

In the present study it was observed that 46 % patients were in the age group of 41 - 50 years, age range was between 33 years to 67 yrs. The mean age of the study population was 46.76 ± 7.39 yrs.

Table: 1 Distribution of patients based on age in Acute Chronic Pancreatitis

Age Group in years	Frequency	Percent
31-40	11	22
41-50	23	46
51-60	14	28
61-70	2	4
Total	**50**	**100**

Table 2: Frequency of N34S Mutation of SPINK1 Gene in ACP patients

N34S Mutation of SPINK1 GENE	Frequency	Percent
Homozygous	1	2.0
Heterozygous	7	14.0
Total	8	16.0

In the present study it was observed that a total of 8 patients (16%) were positive for the mutation, of which 2 % patients with ACP presented had homozygous N34s mutation of SPINK 1 gene and 14 % patient had heterozygous N34S mutation of SPINK 1 gene.

Frequency of N34S mutation of SPINK1 gene in ACP patients

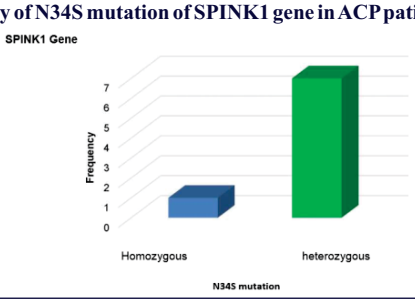

Table3: Comparison of clinical features in relation to SPINK 1 gene

Clinical features	SPINK1 (N34S Mutation) Present		SPINK 1 (N34S Mutation) Absent	
	No.	%	No.	%
Pain Abdomen	7	87.5	37	88.1
Weight loss	3	37.5	8	19
Diabetes	1	12.5	10	23.8
Steatorrhea	3	37.5	11	26.2
Jaundice	0	0	4	9.5
Pseudocyst	1	12.5	7	16.7

In the present study it was observed that there was no statistically significant difference observed in occurrence of clinical features in patients with and without N34S mutation of the SPINK1 gene.

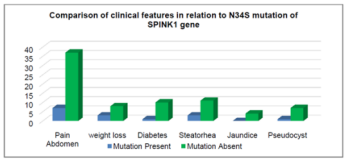

Table 4: Comparison of N34S mutation of SPINK1 gene in between groups

Study group	N	N34S Mutation of SPINK1 gene	
		Yes	No
ACP patients	50	8 (16)	42 (84)
Alcoholic controls	25	2 (8)	23 (92)
ACP patients	50	8 (16)	42 (84)
Healthy controls	25	1 (4)	24 (96)
Alcoholic controls	25	2 (8)	23 (92)
Healthy controls	25	1 (4)	24 (96)

There was no statistically significant difference in the frequency of SPINK gene mutation in between groups.

DISCUSSION

In this study, 50 Alcoholic chronic pancreatitis patients were included. Majority (46%) of the patients were in the age group of 41 to 50 years, age range was between 33 to 67 years.

In our study 100% of patients were male. Studies by Bhasin et al, Chari et al, and reported Barman et al similar finding[6].

In our study steatorrhea was seen in 28% of patients which was similar to a study done by Chari et al who reported 25%, while Panda et al, Bhasin et al, Midha et al[7] & Layer et al showed lower frequency of 5.88%, 6.7%, 6.3% and 12% respectively.

Diabetes was reported in 22% of the patients in our study. This finding was similar to a study by Bhasin et al which reported 22%. In contrast, studies conducted by Panda et al[107] (11.76%), Bhadada et al (11.1%) and Layer et al (8%) reported lower incidence of diabetes and studies done by Chari et al (84%), Balakrishna et al (46.7%), Midha et al (36.3%) and Miyake et al (62%) reported a very high incidence of diabetes[8].

Jaundice was seen in 8% of patients which was close to other studies done by Bhasin et al[8] and Layer et al who reported 10.16% and 5% respectively.

In our study 76% of patients were smokers. The studies done by Midha et al and Balakrishnan et al[9] reported 70.7% and 82% respectively.

In the present study it was observed that in 18% patients duration of alcohol intake was 8 years followed by 16% with history of 10 years intake. The mean duration of alcohol intake in the study population was 10.28 ± 2.35 years and all the patients consumed about 100-150 grams of alcohol per day.

The Pathogenic mechanisms of Alcoholic Chronic Pancreatitis is complex. Recent studies have provided controversial results suggesting the involvement of the N34S mutation of the SPINK1 gene, which occurs with varied frequency in particular populations of patients and plays a variable role in the etiology of different forms of chronic pancreatitis.

In our study, Baseline Clinical characteristics and imaging findings between the groups that were mutation positive and negative were compared. It was observed that there was no statistically significant difference in both clinical characteristics and imaging findings in patients with ACP based on N34S SPINK1 mutation status.

Similar findings were also reported from other studies by Chandak et al[10]. Detailed reports about the clinical characteristics of patients with SPINK1 mutations and alcoholic chronic pancreatitis are very few.

In our study N34S mutation of SPINK1 gene was observed in 1 (4%) healthy control. This finding was consistent with other Indian studies. Bhatia et al,

In our study, there was no statistically significant difference observed in the frequency of N34S mutation of SPINK1 gene in either of the groups. A study from the USA[11] did not find the SPINK1 N34S mutation more commonly in alcoholic Chronic Pancreatitis than in controls 6.25% vs 1.5%.

However, Contrary to our findings the incidence of the mutation in, Polish, Dutch, Finish and German populations showed a marked correlation with alcoholic chronic pancreatitis. Similarly, In India, a study by Chandak et al[12] reported N34S mutation of SPINK1 gene in 26.8% of the patients with alcoholic chronic pancreatitis compared with 2.76% in the control group. However, the mutation occurred more frequently in other groups HP (73%) and ICP (32.5 %) compared with the alcoholic chronic pancreatitis group in this study.

A comprehensive literature research by Aoun et al, showed a strong relationship between the N34S mutation of the SPINK1 gene and idiopathic and tropical pancreatitis and a significantly lower association with alcoholic chronic pancreatitis and therefore concluded from the analysis that alcohol may drive fibrosis primarily through a try p sin-independent pathway.

The results from our study reveals that despite high prevalence, N34S mutation of SPINK1 gene is not associated with alcoholic chronic pancreatitis as there was no statistic significant difference compared to controls. Definite conclusions are not possible due to small sample size studied.

Large sample size and long term follow up are required to address the role of genetics in alcoholic chronic pancreatitis and genotype phenotype correlations. Also, it may be useful to do functional studies of SPINK1 mutation in cell cultures to understand the patho physiology of disease status more completely.

CONCLUSION

- This study was done to assess the prevalence of SPINK1 N34S mutation in alcoholic chronic pancreatitis patients and compare with alcoholics and healthy controls.
- Demographic findings and clinical presentation of alcoholic chronic pancreatitis patients in this study are consistent with majority of Indian studies.
- The prevalence of SPINK1 mutation in Alcoholic Chronic pancreatitis was found to be 16%. Genotype phenotype correlation in alcoholic chronic pancreatitis patients showed no significant difference.
- The prevalence of mutation in alcoholics group and healthy controls were found to be 8% and 4% respectively.
- There was no statistically significant difference observed in the frequency of SPINK1 gene mutation between alcoholic chronic pancreatitis patients and either of the other groups (alcoholics and healthy controls).
- The findings in this study disclose that the SPINK1 N34S mutation is of limited relevance in alcoholic chronic pancreatitis despite its high prevalence.
- The inconclusive results of numerous studies on the associations between the N34S mutation of the SPINK1 gene may result from small study cohorts, which is a crucial limitation in genetic studies.
- Furthermore studies are needed to be done to substantiate the results and to clarify the influence of SPINK1 N34S on the pathogenesis and clinical course of alcoholic chronic pancreatitis.

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