Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 01, 2024

Original research article

CHILDREN WITH CYSTIC FIBROSIS AND PANCREATIC INSUFFICIENCY: PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Introduction and Objectives: Cystic fibrosis is the most common life-limiting genetic condition in Caucasians, affecting 1 in 2500 births. The study examined the percentage of cystic fibrosis patients in paediatric respiratory clinics with pancreatic insufficiency. To compare the clinical and demographic parameters of pancreatic insufficiency and sufficient cystic fibrosis children.

Methods: This study was conducted on children with cystic fibrosis, specifically targeting individuals aged 0 to 15 years. It was an observational study aimed at describing and analyzing the characteristics of the participants. This study was conducted at the, Department of Pediatrics, Ayaan Institute of Medical Sciences, Moinabad, Telangana, India, between the November 2022 to December 2023. Pancreatic insufficiency was established when the faecal elastase level was below 200 micrograms per gramme of stool. The prevalence of pancreatic insufficiency was determined by calculating the percentage along with a 95% confidence interval.

Results: Pancreatic insufficiency was observed in 62.4% of a group of 20 children. The faecal elastase test identified an additional 19% of patients with pancreatic insufficiency compared to relying solely on the standard history of steatoorhoea for diagnosis. All patients experienced recurrent respiratory infections and 78.8% had a weight below the 5th centile on the growth chart. Only a small proportion of patients had additional characteristic symptoms of cystic fibrosis, such as meconium ileus, rectal prolapse, and nasal polyposis. The pancreatic insufficient group had a higher prevalence of foul-smelling stool, frequent bowel movements, and lower Cooperman score, in comparison to both the pancreatic sufficient group. This disparity was shown to be statistically significant.

Conclusions: From the above study it can be concluded two risk factors identified for

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 01, 2024

calculating a clinical score to predict pancreatic insufficiency were a history of foul-smelling stool and frequent bowel movements. To generate this score, a more extensive investigation with a larger sample size will be necessary.

Keywords: Children, cystic fibrosis, pancreatic insufficiency

Introduction

Cystic fibrosis (CF) is a genetic illness that occurs when there is a mutation in the cystic fibrosis transmembrane regulator gene. This mutation causes a malfunction in the transport of chloride in the epithelial cells, leading to a range of clinical symptoms primarily affecting the respiratory system and gastrointestinal tract [1]. Western studies indicate that 85% of children diagnosed with cystic fibrosis experience pancreatic insufficiency. A study conducted in India found that the occurrence of malabsorption among children with cystic fibrosis in north India is 80%. Malnutrition, caused by the loss of pancreatic exocrine function, is negatively associated with lung function, clinical state, and survival. Furthermore, there is scientific evidence demonstrating a strong correlation between pancreatic insufficiency and the presence of both severe pulmonary illness and malnutrition in patients [2].

Therefore, it is crucial to precisely and promptly detect pancreatic insufficiency, address maldigestion, and enhance nutritional status. Diagnosing pancreatic insufficiency in the younger age group of individuals with cystic fibrosis can be challenging. The presence of thick greasy stools and insatiable desire are considered the characteristic features of fat malabsorption [3]. However, it is possible that youngsters may not consistently exhibit these characteristics. In affluent countries, malnutrition and insufficient weight growth are considered reliable clinical indications of pancreatic insufficiency. Nevertheless, there are other more factors contributing to malnutrition and inadequate weight increase among Indian children. This include financial factors, abstaining from certain food products owing to cultural or religious convictions, and the unavailability or lack of acceptance of energy-dense food items. Furthermore, persistent inflammation of the airways and repeated episodes of infection exacerbate the condition of malnutrition [4].

At our hospital, we only screened cystic fibrosis children who exhibited classical symptoms of steatoorhoea for fat malabsorption. Only these youngsters were provided with pancreatic supplements. Our Organisation conducted a pilot study to examine the clinical characteristics of Indian children with CF. the study revealed that only 26.7% of the children exhibited symptoms of fat malabsorption [5]. This is a sharp contrast to the 85% frequency of pancreatic insufficiency in Caucasian children with cystic fibrosis. An investigation involving youngsters from the Northern regions of India and Pakistan revealed an 80% frequency of malabsorption. The disparity may be attributed to the variation in the causal mutation within the Indian population. Another potential explanation is that we may be failing to accurately diagnose primary immunodeficiency when relying solely on clinical characteristics. Therefore, this study aims to determine the actual percentage of PI among Indian children with cystic fibrosis [6, 7].

The stool elastase test, known for its high sensitivity and specificity, is expensive and not commonly accessible. Several small hospitals may lack the capacity to conduct this test. Therefore, it is crucial to establish a scoring system that relies on clinical characteristics and uncomplicated laboratory examinations in order to accurately

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 01, 2024

anticipate pancreatic insufficiency. This technique will be valuable for doctors in distinguishing individuals who exhibit primary immunodeficiency (PI) upon presentation and those who develop PI with the progression of their illness, enabling early intervention [8, 9]. The main aim is to determine the prevalence of pancreatic insufficiency in children with Cystic Fibrosis, aged 0-18 years, who are receiving treatment at a specialized medical facility.

Material and Methods

This study was conducted on children with cystic fibrosis, specifically targeting individuals aged 0 to 15 years. It was an observational study aimed at describing and analyzing the characteristics of the participants. This study was conducted at the, Department of Pediatrics, Ayaan Institute of Medical Sciences, Moinabad, Telangana, India, between the November 2022 to December 2023. Pancreatic insufficiency was established when the faecal elastase level was below 200 micrograms per gramme of stool. The prevalence of pancreatic insufficiency was determined by calculating the percentage along with a 95% confidence interval.

Inclusion Criteria

- High sweat electrolyte >80 mmol/lit in cystic fibrosis children.
- Those diagnosed based on clinical characteristics and borderline sweat electrolytes.

Exclusion Criteria

- Children who were unable to provide stool samples for faecal elastase testing.

Methodology

Children who were diagnosed with cystic fibrosis based on laboratory and clinical criteria from the Paediatric Outpatient department and wards and who visited these areas during the study period were included in the study. Enrollment included individuals who received a new diagnosis throughout the specified period and those who were already known to have cystic fibrosis and attended the review clinic. Agarwal growth charts were utilised to determine the percentiles for height and weight. A recently obtained stool sample was collected specifically for the purpose of examining the levels of faecal elastase. If pancreatic enzyme replacement was not already administered, stool samples were obtained to undergo microscopic inspection for the presence of fat globules.

Results

Table 1: Birth weight distribution

Sr. No.	Birth weight range in grams	Number of Children
1.	1500-2000	1
2.	2001-2500	3
3.	2501-3000	10
4.	3001-3500	6

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 01, 2024

Half of the children included in the study had a birth weight above 2500 grammes. There was only one child who had a significantly low birth weight.

Table 2: Patients' genetic profile

Sr. No.	Mutation	Number of CF children
1.	F508del	1
2.	G551D	0
3.	G542X	0
4.	621G2T	0
5.	M4740V	2
6.	Mutation not detected	9
7.	total	12

12 patients have accessible mutation analysis results. The F508 deletion mutation was identified in 30% of cases. Due to the limited scope of mutation testing, which only covered 3 frequent mutations, and the incomplete sequencing of exons 10 and 11, we were unable to identify the mutation in 61% of cases.

Table 3: Indications of Pancreatic insufficiency

Sr. No.	Symptoms	No.
1.	PS	4
2.	Mod PI	6
3.	Severe PI	10
	Total	20

Extent of pancreatic insufficiency. The prevalence of pancreatic insufficiency was 62.4%, with 41.6% of children experiencing severe pancreatic insufficiency.

Table 4: Comparison between Pancreatic Insufficiency and Foul-Smelling Stool

	FSS present	FSS absent	Total
PI FE <=200	9	2	10
PS FE > 200	1	8	10
Total	10	10	20

Indicates the percentage of children with malodorous faeces among those with cystic fibrosis. A significant majority of children had a documented history of excreting foul-smelling stool.

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Table 5: Comparison of Pancreatic Insufficiency with Abdominal Bloating

	ABN Present	ABN absent	Total
PI FE <=200	6	9	15
PS FE > 200	2	7	9
Total	8	12	20

Children with cystic fibrosis who have insufficient pancreatic function and experience stomach bloating. There was no statistically significant disparity in abdominal bloating symptoms seen between patients with PI and PS.

Table 6: Comparison: Pancreatic Insufficiency versus Inadequate Weight Gain

	Inadequate weight gain	Adequate weight gain	Total
PI FE <=200	10	2	12
PS FE > 200	5	3	8
Total	15	5	20

There was no statistically significant disparity observed between the two groups in relation to insufficient weight gain.

Table 7: Comparison between Pancreatic Insufficiency and Weight Percentile

	0-5 Centile	5-95 Centile	Total
PI FE <=200	15	0	15
PS FE > 200	2	3	5
Total	17	3	20

Assessment of exocrine pancreatic function and weight percentile in patients with cystic fibrosis. All children classified as PI had a body weight below the 5^{th} percentile.

Table 8: Stool microscopy and PI to detect fat globules

	Fat Globules Present	Fat Globules Absent	Total
PI FE <=200	10	3	13
PS FE > 200	3	4	7
Total	13	7	20

83.3% of children with pancreatic insufficiency exhibited many fat globules when examined under a microscope. However, there was no statistically significant distinction compared to children who had normal pancreatic function.

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Table 9: Mortality and extended oxygen therapy

	Death	LTOT
PI (FE<=200)	**2**	**2**
PS (FE>200)	**0**	**0**

Two children in the pancreatic insufficiency group, who required long-term home oxygen, succumbed during the study. Children who had sufficient pancreatic function did not require oxygen therapy at home, and no deaths were documented.

Table 10: Total and percentage of people with CF-related diabetes mellitus

	CFRDM present	CFRDM absent
PI	2	12
PS	0	8

Insulin therapy was necessary for two patients in the group with inadequate pancreas.

Discussion

More and more cases of cystic fibrosis in youngsters from India are being identified and diagnosed, challenging the long-held belief that the disease mostly affects Caucasians. We do not have precise prevalence statistics, but we do have some ballpark figures. Considering India's enormous population, the number of children living with cystic fibrosis could exceed that in many western nations, even if the prevalence is as low as 1 in 40,000, according to an estimate based on migrant population data in the US [8, 9]. Underdiagnosis of the illness despite the presence of classical characteristics is a major issue in India. Increased morbidity, needless and ineffective treatment spending, and accelerated illness progression are all consequences of delayed diagnosis. Pancreatic insufficiency is most commonly caused by cystic fibrosis. Although many gastroenterologists and paediatricians detect pancreatic insufficiency/fat mal absorption, they fail to do a thorough evaluation of the child to rule out cystic fibrosis [10].

The purpose of this prospective observational study was to investigate pancreatic insufficiency in children with cystic fibrosis in India by gathering data from a tertiary care institution. We were able to gather high-quality data on the patients' histories and examinations since the study was prospective. The study was designed to avoid selection bias by recruiting consecutive patients who met the inclusion criteria and used the CF clinical service of the paediatric department [11].

This study aimed to investigate pancreatic insufficiency symptoms in a cohort of children with cystic fibrosis and to determine the prevalence of this condition by use of a sensitive and specific test called faecal elastase. Additionally, we aimed to compare the CF groups with and without pancreatic adequate function in terms of presenting symptoms, lung involvement severity, and other symptoms. Twenty consecutive children with cystic fibrosis (CF) who visited one of our paediatric service locations during the research period were considered for inclusion. Demographic information,

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 01, 2024

illness manifestation, anthropometric indices, and disease severity were all consistent with other case series documented from other regions of India in this population [12, 13].
Among this series, 75% were male. A male predominance is observed in the majority of case series from India. Girls with cystic fibrosis have a lower life expectancy and a worse prognosis than boys with the condition worldwide. We cannot conclude that the larger percentage of boys in this study is a result of superior male survival as this is not an experiment designed to determine the survival benefit of any sex. It might simply be a reflection of how people in general seek medical attention, with boys getting more attention than girls. Out of all the babies born, only one had an extremely low birth weight Studies comparing data from developed countries before and after the implementation of neonatal screening programmes have demonstrated that malnutrition begins during the neonatal period [14, 15].
We also noticed a considerable lag in diagnosis, which is consistent with observations from other sites. Compared to research conducted in New Delhi and Chandigarh, where the average age at diagnosis was 54 and 57 months, respectively, our population had an age of 76 months. After symptoms first appeared, it took an average of 47 months for a diagnosis to be made. A similar finding was made in the study conducted by Kabra *et al*., wherein an average of 44 months elapsed between the beginning of symptoms and the diagnosis. There will inevitably be some variation in the accuracy of the data derived from parents' medical records and histories. Still, it's clear that India's index of suspicion for the condition is low, and that more people should be made aware of this [16-18].
Half of the subjects exhibited airway pseudomonas colonisation when they were recruited. This is in line with a study conducted at AIIMS that found that half of the patients had pseudomonas colonisation in their airway when they were diagnosed. Research conducted in Kashmir revealed that 33.3% of patients had pseudomonas aeruginosa and 33.3% had Staphylococcus aureus colonized with them. We found that the most common clinical features at presentation in our series of children with cystic fibrosis were not gaining weight, having a history of respiratory infections, and possibly malnutrition. This is in line with the statistics from PGIMER Chandigarh, where 94% of the children presented with these symptoms and 74% had recurrent or persistent respiratory tract infections [19-21].
Below, we compare the two groups according to several characteristics in an effort to identify those that characterise the clinical profile of pancreatic deficient individuals and set them apart from PS patients. A statistically significant connection was found between pancreatic insufficiency and a history of foul-smelling stools or increased stool frequency in this series. Statistical significance was not reached, despite the fact that 73 percent of children with PI reported a history of passing large, oily faeces, compared to 33.3% of PS patients. Equally prevalent, in both the PI and PS groups, were patients who had experienced bloating and stomach pain in the past. In comparison to Western diets, the typical Indian diet is lower in fat. Therefore, many PI patients may not report major steatorrhoea symptoms, such as large, greasy stools. We may have to change the wording of the question in future research to see if these are present in children after they eat a fatty meal. There were no changes in symptomatology reported or addressed in other Indian investigations [22, 23].
Insufficient pancreatic patients were diagnosed earlier, yet overall most patients

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 01, 2024

experienced an unsatisfactory delay in diagnosis. In comparison to PS, they were more prone to pseudomonas colonisation, had worse growth, were more likely to have serious lung disease, and require home oxygen therapy. While this study's results did not reach statistical significance, it is highly probable that future research with a larger sample will. Two of the study's participants died due to pancreatic insufficiency. It is not surprising that two patients with exocrine deficiency also take insulin for endocrine pancreatic insufficiency [24, 25].

There is evidence linking pancreatic insufficiency to malnutrition and, by extension, impaired lung function. Bronchiectasis was present in just 40% of the children with PI in our research. This makes sense because bronchiectasis has not yet developed in several of the included participants, who were quite young. We did not use HRCT, the gold standard for diagnosing bronchiectasis in all patients, because it was secondary to our main goal in the study. Nonetheless, we discovered that PI patients had lower scores than PS patients on a clinical score called the Cooperman score, which has a strong correlation with lung function. There was a statistically significant difference here. Our research showed that electrolyte concentrations in sweat were below 100 in 66.6% of pancreatic insufficiency youngsters. Research has shown that children with PI often have low sweat chloride concentrations, which can be explained by the edoema caused by hypoproteinemia [25, 26].

One of the secondary objectives of our investigation was to develop a clinical score to indicate pancreatic insufficiency. Despite the abundance of clinical scores for predicting severity, prognosis, etc. such as the Kanga *et al*. Score, the Switchman Scale, and the NIH Scale-none of these ratings have been found to predict PI, according to the reviewed literature. In underdeveloped nations, where pancreatic function testing are readily available, this might not be a top concern. Inadequate Pancreatic Function While a patient's specific genetic mutation can be predicted using a prevalence score, doing so in underdeveloped nations is prohibitively expensive and out of reach for the vast majority of patients. As a result, Indian clinicians will find clinical scores to be an invaluable resource [27-29].

Conclusions

We were able to detect an additional 19% and provide pancreatic enzyme replacement using the faecal elastase test. There were two deaths in the pancreatic insufficiency group throughout the research period as a result of serious pulmonary illness. They were both homebound on oxygen therapy and under the age of two. There was a statistically significant decrease in the Cooperman score for clinical severity in the pancreatic insufficiency group. The average score of individuals suffering from pancreatic insufficiency. Concerning the degree of malnutrition or pseudomonas aeruginosa colonisation of the airways, however, no statistically significant difference was seen between the two groups.

Funding: None.

Conflict of Interest: None.

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