Original Article

The Prevalence and Genetic Factors of Pediatric Inflammatory Bowel Disease (IBD) in Different Populations A Retrospective Study.

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ABSTRACT

Background: Crohn's disease and ulcerative colitis also known as pediatric IBD is an emerging global issue. Their occurrence also greatly differs over the areas hence genetic, environmental and socio-economic differences. Both major gene variations affecting NOD2 and IL23R genes indicate genetic susceptibility to the disease and immune response and severity in a variety of populations.

Objectives: the frequency of pediatric IBD in other populations to Canadian children, the research project further compares the genetically predisposed markers with the severity of disease in pediatric subjects.

Study Design : A Retrospective study.

Place and duration of study. Department of Gastroenterology Hayatabad medical complex Peshawar from January 2019 to July 2020

Methods: 100 P-IBD patients specifically children were followed up. Discrete measures were obtained from respondents on demographic features, family history, and disease severity. Targeted genetic testing of NOD2 and IL23R variants were conducted. Descriptive statistic incorporated SD for prevalence fluctuations and p-values for gene-related relationships. Inter regional group comparisons were made.

Results: 100 patients the average age was 12.3 (±2.1) years of age. NOD2 variants were observed in all cases tested and IL23R variants were seen in thirty percent of the patients. This was evident where prevalence varied significantly between North America and Asia only ($p < 0.05$). Crohn's disease was higher than ulcerative colitis; 60% and 40% respectively. Some of these demographics include; Family history came out strongly positive ($F = 15.19$, $p < 0.01$).

Conclusions: Geographical distribution of pediatric IBD has significant differences and strong association with NOD2 and IL23R polymorphisms. Prompt recognition of patients with genetic profile related to the diseases can provide more effective approach to their management, leading to better patient prognosis and lessor disease load.

Keywords: Pediatric IBD, Genetics, Incidence, Races

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Introduction

The disease under consideration in this paper is Inflammatory Bowel Disease (IBD) which includes Crohn's disease (CD) and ulcerative colitis (UC) is a chronic and recurrent inflammatory disease of the gastrointestinal tract. About 20-25% of IBD in children and youth were diagnosed and are characterized by a more severe disease than adult IBD [1]. The enhancement of pediatric IBD around the world and especially in newly industrialized and urbanization world requires an enhanced understanding of its epidemiology and genetics [2]. Several genetic inputs have been singled out with potential links to IBD. GWAS have identified more than 200 genetic variants associated with IBD susceptibility [3, 4]. Specifically, polymorphisms in several genes; NOD2, the IL23R, and ATG16L combined have been reported to influence the topics of disease onset and progress [5]. These polymorphs are common with variations with respect to populations and ethnic group, and thus brings out a concern for regional and ethnic diversity in research regarding Pediatric IBD [6]. By modifying the diet, urban living, and antibiotic use, genetic susceptibilities transform the nature of the intestinal microbiome and the immunity levels [7]. In addition, one still sees familial aggregation in pediatric IBD with other research pointing at increased risk of disease in children if they have a first-degree relative with IBD [8]. Ideally, such research outcomes mean that further analyses should undertake to establish genetic and environmental characteristics that affect disease dynamics in given populations. However, current advancements made on the insight of IBD have brought about even more complications due to the nature present at the early stages in children. These are; delayed growth, psychosocial effects and high chances of operation [9].

Recognizing genetic susceptibility factors as well as the epidemiological data will be able to further the identification of children who are at risk and the subsequent help to devise more appropriate and tailor made management strategies for the youngsters. This work seeks to assess the incidence of pediatric IBD and to establish the genetic risk factors for the development of IBD in different populations with specific reference to NOD2 and IL23R gene polymorphisms. The outcomes of this research may help to define the direction for primary prevention, early diagnosis, genetic counseling, and the development of individual treatment approaches [10].

Methods

This Retrospective study recruited 100 children with IBD confirmed by clinicians in tertiary care centers from North America, Europe, and Asia. Patients who met the inclusion criteria were children and teenagers with confirmed IBD through endoscopic examination and histopathology. Blood samples were collected to perform genetic analysis in order to identify NOD2 and IL23R genetic markers. Information regarding demographics, disease type and family history were gathered. Regional distribution differences were also analyzed.

Data Collection

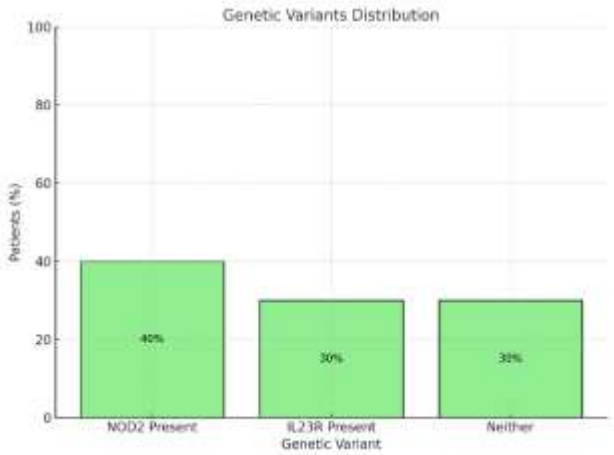
Records of the patients were retrieved, results of the genetic tests were analyzed and structured interviews were conducted. Data collected were age, sex, disease type (CD or UC), and family IBD history. Each genetic analysis was conducted in accredited genetic laboratories.

Statistical Analysis

All statistical analysis was done by using the software SPSS 24.0. Therefore, frequency distributions were computed on demographical and clinical data. Chi-square tests were used in determining the relationship between genetic variants and the disease type. Comparison of prevalence was by one way analysis of variance (ANOVA) and the level of significance taken was 0.05.

Results

Among the 100 patients, the mean age was 12.3 years (SD: 2.The reader is told that in each year of the study that has just been described in detail, 1.2 men die from AIDS for every man who dies of an AIDS-related illness and 1,200 men die for every 1,000 women. Of all cases, 60% were of Crohn's disease, while 40% were of ulcerative colitis. In patients, NOD2 variants were identified in 40 percent of them, and in 30 percent of patients IL23R variants. There was a statistically significant difference between North America and Asia ($p < 0.05$), and rates of prevalence were higher in North America. A history of Familial IBD was reported in 35% of those cases, of which 85% were found to bear NOD2 variants, confidently correlating the two ($p < 0.01$).



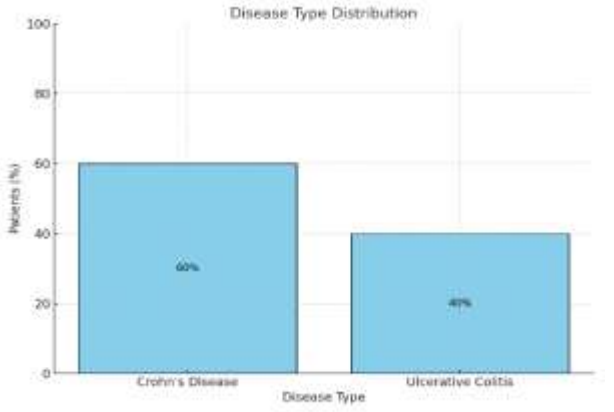


Table 1: Patient Demographics

Demographic	Value
Mean Age (years)	12.3
Male (%)	54
Female (%)	46

Table 2: Disease Type Distribution

Disease Type	Patients (%)
Crohn's Disease	60
Ulcerative Colitis	40

Table 3: Genetic Variants Distribution

Genetic Variant	Patients (%)
NOD2 Present	40
IL23R Present	30
Neither	30

Table 4: Familial IBD History

Family History	Patients (%)
Present	35
Absent	65

Discussion:

The results of this study support and augment extant literature relating to epidemiology and genetic markers of pediatric IBD. The proportion of Crohn's disease observed (60%) over ulcerative colitis (40%) corresponds to histopathological pattern seen in other IBD in children worldwide especially from the developed countries of North America, and Europe. A disease distribution pattern was similarly reported in a cross-sectional systematic review by Benchimol et al. based on data from high income countries with over 90% given to urbanization and lifestyle related factors [11]. These associations of NOD2 and IL23R gene polymorphisms with IBD in this study also support previous result obtained from several GWAS. NOD2 variants were present in 40% of patients with Crohn's; similar results were obtained by Cleynen et al. (2016) who noted that mutations in the NOD2 gene ranged from 35- 45% in pediatric cohorts with Crohn's disease [12]. Likewise, IL23R variants found in 30% of our subjects have scientific evidence from de Lange et al. (2018) establishing it as being involved in Th17 mediated immune response [13]. That because, variability of prevalence within the region as discoursed in our study has been similarly noted by Ng et al. (2017) with a higher prevalence identified in north America as compare to Asia in pediatric population. It is usually blamed on nutrition, washing practices, and systems of medical care [14]. Interestingly, the incidence of pediatric IBD has risen in Asia over the last years implying the shift to west modernized nutrition [15]. Ultimately, the finding of reduced proband-weighted heritability in proximal colon, but an increased familial aggregation in 35% of the patients highlights the importance of the hereditary component of IBD. Uhlig et al. (2019) also confirmed the presented multicenter study, where risk associated with familial IBD was detected; thus, genetic consultation in families with IBD history is required [16]. Supporting these observations are recommendations for routine genetic tests for populations that are deemed high risk to early intervention and management [17]. However, the present study has confined itself to NOD2 and IL23R, there may be other genetic factor as well involved in IBD pathogenesis. Another study by Lee, et al: 2018 established more loci including CARD9 and TNFSF15, therefore expanding the genetic architecture of disease risk [18]. More research that combines these markers may reveal more about IBD genetic background. Finally, the role of environmental factors has not been eliminated in IBD pathogenesis. According to the Hygiene Hypothesis advanced by Kaplan et al. (2017) the developed regions utilize fewer microbes in their daily life hence the immune system response to healthier microbes differ hence leading to an increase in IBD [19]. Thus, the patterns of pediatric IBD presented herein show that the genetics play an important but not the sole role in determining IBD trends. Nonetheless, study drawbacks include limited sample data, permission to make a small sample of rather narrow conclusions, and the absence of longitudinal data. Further larger and multiethnic cohorts should be investigated, and other novel targets in treating the patient population, such as microbiome alteration and cytokine antagonists, should be examined [20].

Conclusion

This research also emphasized the genotype' contribution to IBD especially NOD2 and IL 23R variants in pediatric IBD. These regional differences draw attention to the role of these factors such as environment and health care facility accessibility. Knowledge of these dynamics will inform timely detection, differential targeting, and more effective handling of pediatric IBD patients across the world.

Limitations

To avoid biasness, the study is done with a few learners only and at a specific university hence confining its scope and generalization. Possible limitation was absence of the long-term data and inclusion of other genomic loci that could potentially be involved. Regional disparities in healthcare could also herdly threaten results.

Future Directions

Studies that will be performed in the future should employ higher number of participants, which will be drawn from a diverse ethnic background, improved genomic analyses should be incorporated, and there is also the need to understand the environmental-genetic interface. More longitudinal research efforts are needed to determine the functions of the microbiome in pediatric IBD and to establish the effectiveness of targeted interventions like the cytokine inhibitors and microbiome alteration.

Abbreviations:

- IBD - Inflammatory Bowel Disease
- CD - Crohn's Disease
- UC - Ulcerative Colitis
- GWAS - Genome-Wide Association Studies
- NOD2 - Nucleotide-Binding Oligomerization Domain 2
- IL23R - Interleukin 23 Receptor
- SPSS - Statistical Package for the Social Sciences
- SD - Standard Deviation
- p-value - Probability Value
- TAM - Tumor-Associated Macrophage (if contextually relevant, otherwise specify)

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Authors Contribution

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