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The Rate and Outcome of Sinonasal Disease in Children with Primary Immunodeficiency; Tertiary Hospital Experience

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Abstract

Objectives: To determine the rate, characteristics and outcome of sinonasal disease (SD) among primary immune compromised (PID) pediatric patients.

Methods: Cross-sectional retrospective study. All pediatric patients with primary immunodeficiency aged 18 years or less of both genders, had otorhinolaryngology (ORL) encounter or sinus CT at King Abdulaziz Medical City, Ministry of National Guard Health Affairs (MNGHA), Riyadh between January 2015 and December 2020 were included.

Results: 123 pediatric patients diagnosed with PID between 2015 and 2020. 9 patients were diagnosed with sinonasal disease. Chronic rhinosinusitis with nasal polyposis is the most common type of SD (66.66%). No significant association was found between having SD and bone marrow transplantation (P=0.424). Sinus CT Lund Mackay score was significantly higher in SD (p = 0.005). Endoscopic sinus surgery was carried in 44.44% of patients. 90% were alive and stable by the end of the study.

Conclusion: In conclusion, sinonasal disease constitute major risk of morbidity as well as for mortality in immunocompromised patients. Thus, early detection with high threshold of suspicion should be considered in this critical population.

Introduction

The diagnosis and management of sinonasal disease in immune competent patients is usually straightforward [1] .However, in immune compromised patients, the management can be very challenging because of vague symptoms, paucity of the immune response, and frequent association with aggressive and rapidly progressive infection [2]. In addition, due to the advances in medical field, the number of immune compromised patients is increasing leading to more opportunistic infections by unusual pathogen such as Pseudomonas aeruginosa and fungal agents [3,4].

Fungal sinusitis is classified into non-invasive and invasive sinusitis based on the presence of fungal invasion into the submucosa and adjacent structure [5]. The invasive fungal sinusitis is additionally subclassified into chronic and acute disease, both of which affect patients with some degree of immunodeficiency [5].Chronic fungal sinusitis usually presents with non-acute symptoms such as low-grade fever, facial pain, epistaxis, or nasal congestion over months to years. In contrast, acute fungal sinusitis usually presents rapidly within less than one month period. In addition to the typical sinusitis symptoms, patients may present with visual changes and cranial neuropathies which indicate progression of the disease [3]. However, patients with severe neutropenia frequently present with unspecific symptoms such as fever lasting for more than 48 hours in early stages with other symptoms occurring in later stage leading ultimately to poor prognosis [6].The lack of ability to mount an efficient immune response is thought to be responsible for its relatively high 50% to 90% mortality rate [7].

Early diagnosis and immediate treatment are considered vital for better survival rates [6] .The gold standard for diagnosis of fungal sinusitis is histopathologic examination of nasal biopsies [7]. Middle turbinate biopsy at the time of nasal examination is recommended as a safe and effective method for timely diagnosis. This procedure can be performed either upon patient's admission or in outpatient clinic setting at the time of endoscopic nasal examination [7]. Additionally, cultures are used to identify the offender agents and their antimicrobial susceptibility. Aspergillus and Mucorales are the most commonly isolated pathogens in acute invasive fungal sinusitis (AIFS) [3]. Recently, more rapid and sensitive detection methods, such as in situ hybridization and polymerase chain reaction (PCR), have been used to facilitate immediate diagnosis [4]. Findings on imaging workup are usually not specific in the early stages of the disease and might lead to underestimation of the disease extent. However, they remain critical to assess invasive sinonasal disease and for surgical planning.

Optimal management of sinonasal disease in immune compromised patients requires a multidisciplinary approach [3]. Urgent aggressive surgical debridement with antifungal therapy is the mainstay of treatment in AIFS. In adult population, the main surgical treatment is endoscopic sinus surgery (ESS). Reported success rate is up to 80% with acceptable safety profile. ESS is also used in the pediatric population, but less frequently, and mostly used for chronic rhinosinusitis that is refractory to medical treatment. Outcome is generally satisfactory with success rates in otherwise healthy children ranging from 82% to 100%, and an estimated complication rate of 1.4%. However, limited data are available regarding ESS in immune compromised children [4].

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The purpose of the study is to shed light on the incidence, characteristics, and outcomes of sinonasal disease in pediatric primary immunodeficiency patients and thus facilitate in developing guidelines for evaluation and management in such patients. To the best of the author's knowledge, there are no similar researches addressing this matter in Saudi Arabia.

Materials and Methods

The study was a retrospective cross-sectional study, approved by the local institutional review board (IRB) King Abdullah International Medical Research Center. All pediatric patients with primary immunodeficiency aged 18 years or less of both genders, had Otorhinolaryngologist (ORL) encounter or sinus CT at King Abdul-Aziz Medical City, Ministry of National Guard Health Affairs (MNGHA), Riyadh between January 2015 and December 2020 were included. Patients aged 19 years and above, diagnosed with secondary immunodeficiency were excluded from the study. Demographic, clinical and radiological data were collected in pre-specified form. All data regarding the patient were collected from the patient's electronic record.

The study is based on a structured data collection sheet. The data were entered into excel sheet. The data collection sheet is composed of 14 questions, and divided into 4 domains; patient demographics (gender and age), clinical (presenting symptoms), evaluation (Imaging and pathology), and management (management and outcome).

Statistical Analysis

The demographic and clinical characteristics such as gender, presenting symptoms, and imaging data were presented as frequency and percentage. Age was reported as mean and standard deviation. Rate of sinonasal disease was estimated by dividing the number of patients who had the disease over the total number of patients. Rate was reported along with the corresponding confidence interval.

Fisher exact test was used to association between categorical variables. Mann-Whitney test was also used to test for association as the variable of interest was not normally distributed. Level of significant was set at 0.05.The analysis was conducted by using SAS version 9.4.

Results

1) Demographic and Clinical Characteristics of the Study Cohort

There are 123 pediatric patients who were diagnosed with primary immunodeficiency between 2015 and 2020. 40 patients were seen by ORL physicians during their admission or had sinus CT. From these 40 patients, 19 patients (47.5 %) had combined immunodeficiency, 10 patients had MHC class ll deficiency, 7 patients had severe combined immunodeficiency (SCID), 1 patient had MHC class l deficiency, and 1 patient had Purine nucleoside phosphorylase (PNP) deficiency. 13 patients (32.5%) had phagocytic cell defects where 9 patients had chronic granulomatous disease (CGD), 3 patients had HIES, and 1 patient had leukocyte-adhesion deficiency (LAD). Also 6 patients (15%) had disease of immune dysregulation in which 5 patients had Griscelli syndrome and one patient had familial haemaphagocyticlymphohistiocytosis (HLH). Lastly, only 2 patients had syndrome with immunodeficiency which is CD4 lymphocytopenia (Table 1). Regarding gender, 20 (50%) were female patients and 20 (50%) were male patients (Table 2). 18 patients (45%) had bone marrow transplant. All patients had allogenic bone marrow transplant (Table 3).

2) Demographic and Clinical Characteristics of Patients Developed Sinonasal Disease

Out of these 40 patients included in the study, 9 patients (22.5%) were diagnosed with sinonasal disease (Table 4). Median age for diagnosed patients was 7 years of age, with the youngest patient aged less than 1 year and oldest was 13-year-old (Table 5). 5 patients (55.56%) were male, and 4 patients (44.44%) were female, with no significant gender difference (P=1.00) (Table 6). Chronic rhinosinusitis without nasal polyposis is the most common type of sinonasal disease 6 patients (66.66%). Additionally, one patient with chronic rhinosinusitis (11.11%) with nasal polyposis, one patient with allergic fungal rhinosinusitis (11.11%) and lastly one patient with acute rhinosinusitis (11.11%) (Table 7). Prevalence of sinonasal disease observed between those who had a history of bone marrow transplantation and those who did not is 16.7% (3 patients)compared to 27.3% (6 patients)with no significant association was found between having sinonasal disease and bone marrow transplantation (Table 8). (P=0.424) Nasal obstruction was the most common presenting symptom (33.3%), followed by fever, facial pain, headache, and rhinorrhea (22.22%). Only one patient (11.11%) had facial swelling. None of the patient had sign of ocular involvement such asproptosisnoroculomotornervepalsy (Table 9). Regarding the underlying PID, 6 patients (66.66%) had combined immunodeficiency, 2 patients (22.22%) had phagocytic cell defects, and only one patient (11.11%) had Diseases of immune dysregulation (Table 10).

3) Sinus CT Scan Screening

All of the diagnosed 9 patients with sinonasal disease had CT scan. On the other hand, from the 31 unaffected patients, 27 patients (87.10%) had screening sinus CT. For BMT, 17 patients out of 18 patients (99.44%) had screening sinus CT (Table 11). A significant difference in the mean of Lund Mackay score was observed between those who had sinonasal disease and those who did not ($p = 0.005$). It was observed that those with sinonasal disease had a significantly higher Lund Mackay score compared to those without sinonasal disease (16.89 + 4.78 vs 8.15 + 7.98) (Table 12).

4) Evaluation and Management of Sinonasal Disease (N=9)

Further evaluation for diagnosed patients included nasal swab and biopsy. 6 patients (66.67%) had nasal swab, while 5 patients (55.56%) had nasal biopsy. 3 patients (33.33%) has positive results, 2 patients were bacterial culture while only 1 patient had positive fungal culture. Fungal Aspergillus was the detectable fungal pathogen. Endoscopic sinus surgery was carried out in 4 patients (44.44%) of the total 9 with sinonasal disease. None of the patients was given any antifungal agent (Table 13).

5) Outcome of Patients Included in the Study (N=40)

36 patients (90%) were alive and stable by the end of the study, with no recurrent disease or relapse. However, 4 patients (10%) passed away due to underlying disease with more advanced infections that were not related to sinonasal disease (Table 14).

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Table 1: Type of Primary Immunodeficiency

Type of primary immunodeficiency	Frequency	Percent
Combined immunodeficiency	19 patient (TOTAL)	47.50%
Severe combined immunodeficiency (SCID)	7 patients	17.5%
MHC class ll Deficiency	10 patients	25%
MHC class I Deficiency	1 patient	2.5%
Purine nucleoside phosphorylase (PNP) deficiency	1 patient	2.5%
Phagocytic cell defects	13 patients	32.50%
Chronic granulomatous disease (CGD)	9 patients	22.5%
Hyper IgE syndrome (HIES)	3 patients	7.5%
leukocyte-adhesion deficiency (LAD)	1 patient	2.5%
Diseases of immune dysregulation	6 patients	15%
Gris celli syndrome	5 patients	12.5%
Familial haemaphagocyticlymphohistiocytosis (HLH)	1 patient	2.5%
Syndrome with immunodeficiency	2 patients	5%
CD4 lymphocytopenia	2 patients	5%

Table 2: Gender

Gender	Frequency	Percent	Cumulative	Cumulative
			Frequency	Percent
Female	20	50	20	22.5
Male	20	50	40	100

Table 3: Patient Underwent Bone Marrow Transplant

BMT	Frequency	Percent	Cumulative	Cumulative
			Frequency	Percent
Done	18	45	18	45
No done	22	55	40	100

Table 4: Patient Developed Sinonasal Disease

Sinonasal disease	Frequency	Percent	Cumulative	Cumulative
			Frequency	Percent
Yes	9	22.5	9	22.5
No	31	77.5	40	100

Table 5: Age at Presentation

Sinonasal disease	Frequency	Percent	Cumulative	Cumulative
			Frequency	Percent
Yes	9	22.5	9	22.5
No	31	77.5	40	100

Table 6: Gender of Patient Developed Sinonasal Disease

Sinonasal disease	Frequency	Percent	Cumulative	Cumulative
			Frequency	Percent
Yes	9	22.5	9	22.5
No	31	77.5	40	100

Table 7: Type of Sinonasal Disease

Type of sinonasal disease	Frequency	Percent
chronic rhinosinusitis without nasal polyposis	6 patients	66.66%
chronic rhinosinusitis with nasal polyposis	1 patient	11.11%
Allergic fungal rhinosinusitis	1 patient	11.11%
Acute rhinosinusitis	1patient	11.11%

Table 8: The Association between The Presence of Sinonasal Disease and Bone Marrow Transplantation

Type of sinonasal disease	Frequency	Percent
chronic rhinosinusitis without nasal polyposis	6 patients	66.66%
chronic rhinosinusitis with nasal polyposis	1 patient	11.11%
Allergic fungal rhinosinusitis	1 patient	11.11%
Acute rhinosinusitis	1patient	11.11%

*Significant at level 0.05

Table 9: Presenting Symptoms

Type of sinonasal disease	Frequency	Percent
chronic rhinosinusitis without nasal polyposis	6 patients	66.66%
chronic rhinosinusitis with nasal polyposis	1 patient	11.11%
Allergic fungal rhinosinusitis	1 patient	11.11%
Acute rhinosinusitis	1patient	11.11%

Table 10: Type of Primary Immunodeficiency in SinonasalDisease Patients

Type of sinonasal disease	Frequency	Percent
chronic rhinosinusitis without nasal polyposis	6 patients	66.66%
chronic rhinosinusitis with nasal polyposis	1 patient	11.11%
Allergic fungal rhinosinusitis	1 patient	11.11%
Acute rhinosinusitis	1patient	11.11%

Table 11: Sinus CT Scan Screening

Type of sinonasal disease	Frequency	Percent
chronic rhinosinusitis without nasal polyposis	6 patients	66.66%
chronic rhinosinusitis with nasal polyposis	1 patient	11.11%
Allergic fungal rhinosinusitis	1 patient	11.11%
Acute rhinosinusitis	1patient	11.11%

Table 12: Lund Mackay Score

Type of sinonasal disease	Frequency	Percent
chronic rhinosinusitis without nasal polyposis	6 patients	66.66%
chronic rhinosinusitis with nasal polyposis	1 patient	11.11%
Allergic fungal rhinosinusitis	1 patient	11.11%
Acute rhinosinusitis	1patient	11.11%

*Significant at level 0.05

Table 13: Evaluation and Management of Sinonasal Disease

Type of sinonasal disease	Frequency	Percent
chronic rhinosinusitis without nasal polyposis	6 patients	66.66%
chronic rhinosinusitis with nasal polyposis	1 patient	11.11%
Allergic fungal rhinosinusitis	1 patient	11.11%
Acute rhinosinusitis	1patient	11.11%

Table 14: Outcome of Patients Included in the Study (N=40)

Screening_CT	Frequency	Percent	Cumulative	Cumulative
			Frequency	Percent
Stable	36	90	36	90
Death due to underlying disease	4	10	40	100
Death due to sinonasal disease	0	0	0	0
Relapse sinonasal disease	0	0	0	0

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Discussion

This study offers insight into the occurrence, features, and outcomes of sinonasal illness in children with primary immunodeficiency. To the best of our knowledge, no analogous studies have been conducted in Saudi Arabia. The study's findings demonstrate the guidelines for evaluating and managing sinonasal illness in immune compromised pediatric patients. This study comprised 40 individuals who had sinus CT scans performed or been seen by ORL physicians.

Primary immunodeficiency disorders (PID) refer to a heterogeneous group of disorders characterized by defect in one or more components of the immune system [8]. Most of PID result from inherited genetic defects; however some diseases are not yet defined at the molecular level. In these cases, the disease is considered primary only if all other potential contributors to immune dysfunction such as viral or bacterial infections, malnutrition, or immunosuppressive drugs have been excluded [8]. According to American Academy of Allergy, Asthma, and Immunology, PID are broadly classified into combined B- and T-cell immune deficiencies, well-defined syndromes with immunodeficiency, predominantly antibody deficiencies, diseases of immune dysregulation, congenital defects of phagocyte, defects of innate immunity, auto inflammatory disorders, and complement deficiencies [9].In this study most of the affected patients (66.66%) with sinonasal disease had combined immunodeficiency.

There were 20 (50 %) male patients and 20 (50 %) female patients. Only 18 individuals (45 %) had a bone marrow transplant. However, only 9 (22.5 %) of the 40 patients were diagnosed with the sinonasal illness. The diagnosed patient's median age was seven years, with the youngest patient being less than 1 year-old and the oldest being 13 years of age. Similarly, a study conducted in 2017 by Amit Ritter showed that immune suppressed pediatric patients with a mean age of 9.5 year had acute rhinosinusitis [4]. Although a difference in the prevalence of sinonasal disease was observed between those who had a history of bone marrow transplantation and those who did not (16.7% vs 27.3%), no significant association was found between having sinonasal disease and bone marrow transplantation. (P=0.424)

According to our findings, nasal obstruction was the most prevalent presenting symptom (33.3%), followed by fever, face pain, and rhinorrhea (22.2 %). The least reported symptoms in this study were nasal discharge and difficulty breathing [10]. Only one patient (11.11 %) had facial swelling, which has previously been found to be strongly indicative of acute invasive fungal rhinosinusitis (AIFR) [4], yet none of the patient in this study developed AIFR. In contrast, study in pediatric immune competent conducted by Alshehri et al. in Saudi Arabia in 2021 found that fever was the most commonly reported complaint (50%), followed by red eye (44%), runny nose (42%), cough (41%), and headache (36 %).10 However most studies in pediatric immune compromised patients showed that fever was main presenting symptom.[4,11] On the other hand, 3 patients were asymptomatic in this study suggesting that the absence of fever does not rule out sinus infection.

While histopathology is the gold standard for diagnosing sinonasal illness, paranasal sinus computed tomography (sinus CT) is very useful and informative tool for diagnosis and effective surgical planning. [12,13] However, in the early stages of the disease, it displays nonspecific alterations such as unilateral enlargement of the nasal cavity or paranasal sinuses. The nuclear magnetic resonance imaging (MRI) is critical when the orbital or cranial invasion is suspected [14]. In our study, nine diagnosed patients received CT scans, whereas 27 patients (87.10 %) received screening sinus CTs. This suggest that most immune compromised patients get full investigations including sinus CT during hospital admissions to rule out invasive infections, specially for patients who don't have specific symptoms. The mean Lund Mackay Score in our diagnosed patients was 16.88 compared to 8.15 of unaffected patients.

Culture investigations are also helpful in identifying the species responsible for sinonasal illness.[4,15] However, the diagnostic usefulness of these species is mainly restricted by their slow growth rate, particularly for fungal infections.[4] Direct microscopy and Histopathological results are faster alternatives, although species identification is more challenging with these approaches.[16,17] Only three patients (33.33 %), in our study got positive microbial infection findings, i.e., two patients had a bacterial infection while only one patient had a fungal infection. That is why mortality in this study was related to underlying diseases rather than bacterial or fungal infection, as in AIFR. Likewise, study in adult immune compromised patients showed similar detection rate where (36%) of the patients had positive culture results [6] .The detected fungal species in our study was Aspergillus spp which is in accordance with previous studies [18, 19, 20]. These microorganisms are saprophytes that may be found in degraded materials, soil, and fruits, as well as in healthy people's throats, nasal cavities, and feces. However, they can become pathogenic in immune compromised patients [12,21]. Lastly, none of the patients were given any antifungal agent.

Endoscopic debridement was performed based on clinical and imaging results. 4 patients out of 9 (44.44 %) underwent endoscopic sinus surgery, which was effective in terms of no recurrent disease or relapse. 36 patients (90%) were alive and stable by the end of the study while 4 patients (10%) passed away due to underlying disease rather than sinus related infection. High survival rate explained by the fact that none of the patient had AIFR compared to other study where survival rate was only (49.7%) [20].The degree of immunosuppression and the state of the underlying illness have previously been linked to the prognosis and mortality of AIFR. BMT is a risk factor for fatal fungal infections [12, 22, 23]. where one study reported survival rate was only 57% in 14 bone marrow transplant recipients, including 6 pediatric patients, affected with invasive sinonasal aspergillus.22 However, in the present study even though 17 out of 18 BMT patients (99.44 %) had screening sinus CT; BMT was not risk factor to develop sinonasal disease.

Conclusion

In conclusion, sinonasal disease constitutes a major risk of morbidity as well as for mortality in immune compromised patients. However, they may be under-diagnosed in pediatric immune compromised patients as they tend to be asymptomatic and usually present as either acute invasive ones or in late chronic subtype. Thus, early detection with low threshold of suspicion should be considered in this critical population. This could be achieved by having a screening sinus CT in their early disease course. This will

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help in early appropriate investigations such as cultures and biopsies and further required surgical and medical management and finally a better prognosis.

Author Contributions

Malak Almalki was involved in the data collection, and in writing the original draft of the manuscript. Fahad Alsaabwas involved inmethodology, reviewing, and editing of the manuscript. Fayhan Alroogiwas involved in reviewing the manuscript. Naila Shaheen was involved in statistical analysis. Salwa AlHumaid was involved in writing, reviewing, and editing of the manuscript

Ethics Statement

This study was approved by approved by the local institutional review board (IRB)King Abdullah International Medical Research Center.

Data Availability

The data that support the findings of this study are available from the corresponding author, [Almalki MA] upon reasonable request.

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