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. H \ Z R U G V Rheumatic heart disease; Pulmonary hypertension

$ E E U H Y L D W L R Q V ARF: Acute Rheumatic Fever; AR: Aortic Regurgitation; AS: Aortic Stenosis; CCBs: Calcium Channel Blockers; CHF: Congestive Heart Failure; ECG: Electrocardiography; JUMC: Jimma University Medical Center; LVH: Left Ventricular Hypertrophy; MR: Mitral Regurgitation; MS: Mitral stenosis; NHYA: New York Heart Association; PA: Pulmonary Artery; PAH: Pulmonary Arterial Hypertension; PDEIS: Phosphodiesterase Inhibitors; PH: Pulmonary Hypertension; PVR: Pulmonary Vascular Resistance; RHD: Rheumatic Heart Disease; RVH: Right Ventricular Hypertrophy; TR: Tricuspid Regurgitation; WHO: World Health Organisation

Introduction

Pediatric pulmonary hypertension (PH) (pulmonary hypertension is pulmonary arterial pressure 25 mmHg which is measured indirectly by tricuspid regurgitation pressure gradient through transthoracic echocardiography) is high blood pressure in the arteries of the lungs (the pulmonary arteries). PH is a progressive disease where the pulmonary arteries continue to shrink, making the right side of the heart work harder as it makes the higher pressure needed to force blood through the narrowed arteries [1]. In severe cases of pediatric PH, the small blood vessels in the lungs are damaged to the point they are lost, is happens because the muscle in the arteries

contracts (vasoconstriction) and the artery muscle cells divide and plug up the arteries (muscle cell proliferation). vessels can also become blocked with blood clots or the lungs can become damaged by illness.,is causes the loss of air spaces and blood vessels in the lungs. PH may cause the right side of child„s heart to become enlarged and eventually can cause right heart failure [2]. Pulmonary hypertension (PH) is a rare disease that can present in newborns, infants, and children and is associated with considerable morbidity and mortality. ,e etiology and presentation of PH varies substantially between children and adults. Unfortunately, the lack su…cientcontrolled studies in children makes PH management challenging, with most therapeutic strategies based on extrapolation from adult studies and expert consensus [3]. Pulmonary hypertension (PH) is a frequent complication ofle€ heart disease arising from a wide range of cardiac disorders. In the clinical classi†cation,PH associated with le€ heart disease isclassi†edas Group 2, which includes le€ heart systolic dysfunction, le€ heart diastolic dysfunction and le€ heart valvular disease. Rheumatic mitral valve disease is the most common cause of PH in le€ heart disease, particularly in pediatric patients [4,5].

Statement of the problem

As the incidence of these conditions is increasing, the number of patients presenting with PH is also increasing and today, heart disease represents the most frequent cause of PH.development of PH in patients with le€ heart disease is associated with poor prognosis. However, despite the increasingly large number of patients affected and the impact of PH on outcome, there are currently no speci†c treatment options for these patients [6]. Pulmonary hypertension constitutes a major burden in sub-Saharan Africa. Beside forms of PH prevalent elsewhere there are several risk factors affecting particularly children in this continent, namely: Untreated Congenital Heart Disease, Rheumatic Heart Disease, Endomyocardial Fibrosis, Infections: HIV/AIDS, Tuberculosis, Schistosomiasis, Sickle Cell Disease, Passive Indoor Smoking & Traditional Medication [7].

In sub-Saharan Africa the prevalence of RHD is high due to di‡erent factors.,is fact is true for Ethiopia, where RHD constitute majority of the acquired heart disease in pediatric patients. Even though, there are no studies, it is estimated that PAH related to RHD occurs frequently in such patients and is one of the major causes of morbidity and mortality among those children. Due to…culties in diagnosing PAH, the burden of it among pediatric patients with RHD is undermined in these areas. In Ethiopia, as part of sub-Saharan Africa, this fact is true. According to di‡erent studies the prevalence of RHD is estimated to range from 49.4 - 59.4% [8,9]. Unlike that of developed countries where PH is mainly caused by CHD, it is believed that RHD is the primary cause of PH.

Significant of the study

Since there is scarcity of available data, the aim of this study is to determine the prevalence of PAH, associated comorbidities and treatment practices in pediatric patients with RHD at JUMC and †nally forwards some recommendation for its prevention and better treatment. In addition, this study will serve as a base for future studies to be conducted on pediatric pulmonary hypertension around the country.

Literature Review

Pediatric pulmonary hypertension is a relatively rare, often rapidly progressive disease with varied etiologies that is associated with signi†cantmorbidity and mortality. In fact, until recently, virtually all patients with this condition died within a few years of diagnosis. incidence and prevalence of PAH were estimated to be 2.4-7.6 cases/million/year and 15-26 cases/million, respectively, in large population studies. Worldwide prevalence is hard to appraise, but it is surely underdiagnosed [10],ough epidemiological data are scare on the prevalence of PH in pediatric patients with RHD, it remains a major cause of morbidity and mortality. According to the journal of American college of cardiology the yearly incidence rate for PH were 63.7 per million children [11],ere are no enough data on the prevalence or incidence of PAH associated with RHD in Africa. Some studies estimate a higher prevalence of PAH in those pediatric patients having RHD. In a prospective, multinational cohort done in 4 African countries 11 pediatric cases with an age range of 1 to 17 years (8 females) captured by the registry [12].e pharmacological management with di‡erent causes of PAH was reviewed in that study. Overall, loop diuretics were most commonly prescribed (89% of all cases). Alternatively, none of the cohort patients received home oxygen. Only a small proportion received advanced therapy such as a Phosphodiesterase-type-5 inhibitor (3%) [12].

,e disease is more severe and malignant in sub-Saharan Africa for reasons that are unclear, causing early mitral and/or aortic disease that leads to pulmonary hypertension if untreated. In Cameroun secondary PH occurs in 20% of patients, In Kenya PH is the most common complication of mitral disease, PH is present in 20% of newly diagnosed RHD in South Africa, Severe PH in 61% of patients submitted to surgery in Mozambique [7,13,14]. research done in Uganda have found PH in 291 (77.4%) of the 376 studied patients measured indirectly by TR pressure gradient 30 mmHg in the absence of RVout ow tract obstruction [15]. In a prospective registry which enrolled 3343 patients (median age 28 years, 66.2% female) presenting with RHD at 25 hospitals in 12 African countries (including Ethiopia), India, and Yemen between January 2010 and November 2012, the prevalence of PAH was 28.8% [16]. According to the study done in Jimma, Ethiopia, in which 254 children were included in 5 years retrospective analysis, the prevalence of RHD accounts for 74.1% of the acquired heart diseases. In this study the prevalence of PH was studied as a separate entity and constitute 3.4% of the acquired heart disease [17]. However, there is no proper documentation in Ethiopia regarding the prevalence of PH associated with RHD.

Objective

General objective

To determine prevalence and associated factors of patients with RHD among pediatric patients who have follow up at cardiac clinic at JUMC from January 2014 to August 2017.

Specific objectives

1)To determine prevalence of PAH in pediatric patients with RHD having follow up at JUMC

2) To determine factors associated with PAH in pediatric patients with RHD having follow up at JUMC

3) To assess treatment practices of PAH in pediatric patients with RHD having follow up at JUMC

Research Methodology

Study area

,is study will be conducted in JUMC pediatric department. JUMC is the only referral hospital in south west and gives service for more than 12 million inhabitants of south west Ethiopia.e. center has 4 major departments and other minor departments. department of pediatrics and child health is one of the major departments, and it provides in-patient and out-patient services. pediatric follow up clinics are amongst the out-patient services, one of this being pediatric cardiac clinic, which provides services on a regular weekly follow up basis.

Study period

,e study was conducted from 25th September to 06th October, 2017.

Study design

A cross sectional design was employed.

Population

Source population: All pediatric patients who have RHD and having at least one follow-up at the pediatric cardiac clinic of JUMC from January 2014 to August 2017.

Study population: All children with echocardiography proven cardiac valve lesion secondary to rheumatic heart disease during January 2014 to August 2017.

Sample size and techniques

In determining the sample size particular attention was given to getting adequate sample size that would ensure the generalization of the study †ndings. To a‡ect this, the following assumptions and a standard sample size calculation formula are used to determine the number of RHD cases to be reviewed for the study.

Assumption

A relevant variable to the study under consideration i.e. the prevalence of PAH in RHD from a similar hospital-based study X% or no similar study is identi†ed, but study in some Africa was taken as base line, then p is 77%. Margin of error (d) = 0.05, with 95% con†dence level

$$N = \frac{Z^2 . P(1-P)}{d^2}$$

Taking p=0.77 from previous studies in sub-Saharan region of the prevalence of PAH-RHD [15]. Con†dence level (CI) = 95%

$$N = \frac{1.96^2 \times 0.77(1-0.77)}{0.05^2}$$

N = 272

Sampling methods not used and all records of children with RHD, who were seen during the above time period, medical record number was retrieved from logbook.

Measurement

Variables

Dependent variables: Prevalence of PAH

Independent variables: Age, Sex, Residency, Heart Failure at presentation, Type/s of valve lesion, Comorbid illnesses, Secondary prophylaxis, Echocardiography, Treatment practice

Data collection

Data was collected by using a pretested checklist which was prepared by principal Investigator. All relevant data were collected by chart reviewing and all answers were recorded.

Data analysis

A pretested checklist was used to extract the data and once completeness is checked, it was entered and analyzed using SPSS for windows version 20. Descriptive statistics of categorical variables is presented by frequencies and percentage and mean, and standard deviations will be estimated for continuous variables. Chi square test were performed to identify association between independent variables and pulmonary arterial hypertension.

Results

A total of 280 medical records were approached in the study, of whom 33 were excluded (15 cases had not started follow up, 11 has no echocardiography report and 7 cases had an alternative diagnosis). Medical records of 247 children (41.7% male and 58.3% female) were reviewed thoroughly. 92 (37.2%) were in the age range of 5 to 9 years, while children in the age range of 10 to 14 years were 136 (55.1%) and those 15 years and above were 19 (7.7%). average age of children at first follow up was 10.48 Š 2.98 years. 168 (68%) of the children came from rural area while the rest 32% were from urban areas. Mitral valve involvement was seen in almost all cases of the children, accounting 99.5%, followed by combination of mitral and aortic valve involvement 150 (60.7%).

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Table 1: Sex distribution and residency of pediatric patients with PAH-RHD on follow up at JUMC cardiac clinic, July 2017, Jimma, Oromia, Ethiopia.

Mitral regurgitation was the most common lesion seen in 234 (94.7%), then aortic regurgitation 150 (60.7%), mitral stenosis 67 (27.1%), aortic stenosis was seen in only 5 (2.0%) of the children.

Pulmonary hypertension associated with rheumatic heart disease occurred in 149 (60.3%) of the children on follow up. Among those who developed PAH 86 (57.7%) had mild PH and the rest 63 (42.3%) was found to had severe PH. 88 (59.1%) of the children who had PAH were females and 99 (66.4%) were from rural areas. ,e average TR pressure gradient among those who developed PH was 51.17 Š 18.67 mmHg (Table 1).

,e average age at the diagnosis of PH was 10.73 Š 2.837 years. Of those who developed PAH children aged 5-9 years were 46 and account for 30.8%, 10-14 years 94 (63.1%) and those 15 and above were 9 (6.1%). Among children who are aged 5-9 years 50% developed PAH and 69.1% of children aged 10-14 years developed PAH; this was found to be statistically signi†cant (p=0.007) (Figure 1 and Table 2).

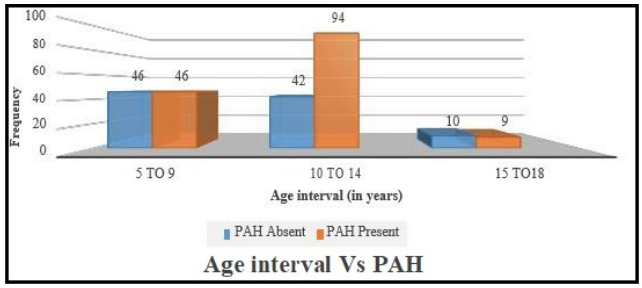

Figure 1: Age distribution of pediatric patients with PAH - RHD on follow up at JUMC cardiac clinic, July 2017, Jimma, Oromia, Ethiopia.

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Table 2: Frequency distribution of age, sex and residency among pediatric patients with PAH - RHD on follow up at JUMC cardiac clinic, July 2017, Jimma, Oromia, Ethiopia.

Heart failure was the presenting illness in most of the children having PAH than those without PAH. 103 of 149 children has heart failure at the time of presentation, accounting 69.1%. Among those children with severe PAH, 45 (71.4%) had heart failure at time of presentation. However, this was seen in only 23 children (23.5%) who do not PAH. And there is a statically signi†cant association between PAH and HF at †rst time of presentation to the hospital (p<0.001) (Table 3).

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Table 3: Frequency of heart failure at the time of presentation in pediatric patients with PAH - RHD on follow up at JUMC cardiac clinic, July 2017, Jimma, Oromia, Ethiopia.

All (100%) patients was taking Byzantine penicillin G as a secondary prophylaxis, on monthly base. Despite this there were a total of 45(18.2%) rheumatic recurrence cases from the study population and among this 32 (71.1% of all the rheumatic recurrences) was seen in those children having PAH. All associated comorbidities were more prevalent in children with PAH than those without PAH. Malnutrition 39 (26.2%) being the commonest associated illness, followed by pneumonia 22 (4.8%) and rheumatic recurrence 14 (9.4%) as a single entity. 34 (22.8%) of children had more than one comorbidity at a time or in separate times. And only 24 (16.1%) of the children with PAH - RHD were found to have no associated illness (Figure 2).

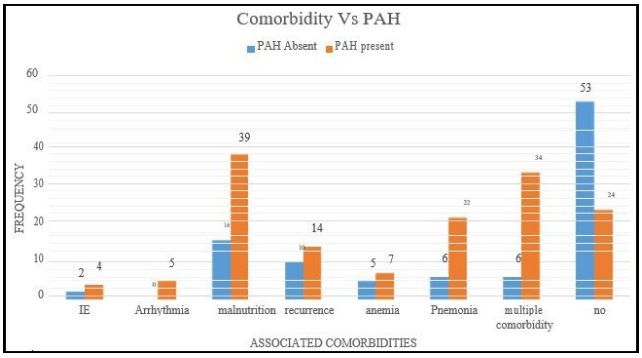

Figure 2: Comorbid conditions in pediatric patients with PAH - RHD on follow up at JUMC cardiac clinic, July 2017, Jimma, Oromia, Ethiopia.

Mitral regurgitation was the most common valve lesion associated with PAH as an isolated or mixed involvement. Mixed Mitral and Aortic valve involvement was seen in 93 (62.4%) of children, there were 137 (91.9%) cases of MR among those who developed PAH. 32.8% of children with mild MR developed PAH, while 80.6% of children with severe MR developed PAH, and this was found to be statistically signi†cant (p Œ0.001). Aortic regurgitation was evident in

96 (64.4%) of children with PAH. 52.4% among Mild AR, 80% among Moderate AR and 78% among severe AR had PAH and there was signi†cantassociation between the severity of AR and the prevalence of PAH (p=0.01). Severity of aortic regurgitation has a signi†cant association with the presence of PAH (p=0.001). Mitral stenosis was found in 59 (39.5%) of children with PAH. Of those children with Mild MS 56.2%, Moderate MS 90.9 and all with Severe MS has developed PAH and this was also statistically signi†cant(p Œ 0.001) (Table 4).

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Table 4: Echocardiography †ndings in pediatric patients with PAH - RHD on follow up at JUMC cardiac clinic, July 2017, Jimma, Oromia, Ethiopia.

Most patients were getting diuretics mainly Furosemide as a single or combined with other drugs. 142 (95.3%) of those children who had PAH was given diuretics alone or combined with other medications. 71 (47.6%) of the patients was given diuretics combined with ACEIs (mostly Captopril and few gets Enalapril). Anti-in‹ammatory medications (either ASA or Prednisolone or both) were also given for patients who developed rheumatic recurrence while on follow up. Among those children who developed PAH only 1 was not given a medication, as compared to 36 (36.7%) of children without PAH. ,ere was only 1 patient who had undergone surgery (Mitral Valve balloon Valvoplasty) for Severe MS, and he had a signi†cantreduction in the TV Pressure gradient, 31 and 8 mmHg before and after the surgery, respectively (Figure 3).

Discussion

ere is general scarcity of published data related to childhood RHD in the African countries that are most a‡ectedby the disease. is study aimed to describe prevalence, associated comorbidity and treatment of PAH among children with RHD and to explore the relationship between the severity of valvular dysfunction, age and heart failure at presentation with PAH. PAH was prevalent in 149 (60.3%) of children, where 63 (42.3%) had severe PAH, with mean age of 10.73 Š 2.837 years and female predominance (59.1%) is comparable with the research among children done in Uganda, 291 (77.4%) of the 376 children studied with mean age of the children was 11.0 Š 2.7 years [15]. A study done in 14 developing countries among children and adults show 28.8% of prevalence, which may be due to the di‡erence in the study population and the treatment given in earlier ages [16]. Other study done among adults and in Southern Yemen show the prevalence to be 80.4%, which may be due to a late presentation to medical attention, mean age was 28.6 Š 14.5 years [18]. Female predominance was also seen in all of the literatures [15-18]. ,e prevalence of PAH is a‡ected by the age of the children at presentation when corrective treatment is not done, and the study showed this association with p value of 0.007.

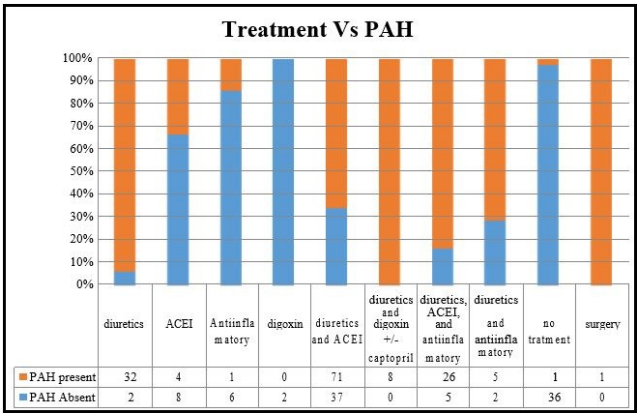

Figure 3: Treatment practice in pediatric patients with PAH - RHD on follow up at JUMC cardiac clinic, July 2017, Jimma, Oromia, Ethiopia.

Most of the children, 103 (69.1%) had heart failure at presentation. Even if there is no data on the prevalence of heart failure among children with PAH - RHD, this †nding is relatively higher from that of the study done in low income sub-Saharan African countries (children and adults who had RHD) showing 43.0% prevalence [16], the di‡erencecan be due to the late presentation in this group. ,e presence of PAH is associated with heart failure at presentation (p<0.001). Mitral valve was the most commonly involved valve 100% alone or combined with aortic valve, Mixed Mitral and Aortic valve involvement was seen in 93 (62.4%) cases. Similarly, in the Uganda study of children with RHD, all except one of the 376 cases studied had mitral valve disease (MR or MS). Severity of Mitral Regurgitation, Mitral Stenosis and Aortic Regurgitation was found to have statistically signi†cantassociation with p Œ 0.05.

Medications were almost the only treatment modality, given to 147 (98.6%) children and a single child got a surgical repair. is very low as compared with 34.8% operation in patients with RHD (children

and adults) in Southern Yemen [18]. ,is difference can be due to the absence of surgical intervention all over the country, until a very recent time. According to the standard treatment guidelines for patients with RHD, which is surgical management of the involved heart valve either by repair or prosthetic replacement, the practice in the study population was found to be almost absent.

Generally, the study has identified the higher prevalence of PAH among children with RHD, which make them more susceptible to acquire heart failure and associated comorbidities. ,e involvement of heart valves is similar with what is known from studies done previously and severity can greatly affect the presence of PAH. However, the practice of the definitive management for children with RHD is poor and needs a better attention to prevent the occurrence of PAH.

Limitation of the Study

,e biggest limitation of this study was the retrospective design - this is inevitably complicated by some incomplete data and lost records. ,e absence of previously published literature on the topic makes it difficult to compare and discuss some of the results.

Conclusion and Recommendations

Rheumatic heart disease related pulmonary hypertension is still the major problem in the center and mitral valve is the commonest valve to be affected. Age is one of the determining factors of development of PAH among children with RHD, as that of severity of heart valve lesion. Children with heart failure at presentation are at increased risk of having pulmonary hypertension. Only one patient was operated for underlying valvular lesion. Further study is needed to assess the reason for late presentation and the difficulty towards the standard treatment practices for children with rheumatic heart disease before the development of pulmonary hypertension.

Ethical Considerations

Prior to data collection official letter was written from Jimma University students research program to the card record office of JUMC. After getting permission data collection was started and patient confidentiality were kept throughout the study.

Conflicts of Interest

,ere are no conflicts of interest for the present study.

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