Prevalence of congenital heart disease-related pulmonary arterial hypertension among the children with congenital heart disease attending follow-up clinic at TASH. Echocardiograph diagnoses.

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Lists of abbreviations

CHD –congenital heart diseases

LA-left atria

LV-left ventricles

PA-pulmonary artery

PAH-pulmonary arterial hypertension

PH-pulmonary hypertension

PHVD –pulmonary hypertension vascular diseases

PAP-pulmonary arterial pressure

Qp-pulmonary blood flow

sPAP -systolic pulmonary arterial pressure

RA –right atria, RV –right ventricle, Rp-pulmonary resistance

Operational definition.

A. Eisenmenger's syndrome(fixed-PAH)

Includes all systemic-to-pulmonary shunts due to moderate to large defects leading to a severe increase in PAH and resulting in a reversed (pulmonary-to-systemic) or bidirectional shunt.

B. Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts(Flow related PAH)

These are patients with moderate to large defects, the increase in PVR is mild to moderate, systemic-to-pulmonary shunt is still largely present, and no cyanosis is present at rest.

C. Pulmonary arterial hypertension with small a defects

In cases with small defects (usually ventricular septal defects< 1 cm(<half of aortic root diameter)and atrial septal defects <2 cm of effective diameter assessed by echocardiography) the clinical picture is very similar to idiopathic PAH.

D. Pulmonary arterial hypertension after corrective cardiac surgery

In these cases, congenital heart disease has been corrected but PAH is either still present immediately after surgery or has recurred several months or years after surgery in the absence of significant post-operative residual congenital lesions or defects that originate as a sequel to previous surgery.[1]

Arbitrary criteria for estimating the presence of PH based on tricuspid regurgitation peak velocity and Doppler-calculated PA systolic pressure at rest (assuming a normal right

atrial pressure of 5 mmHg) and on additional echocardiographic variables suggestive of PH Class a Level b if available.[1]

1)**Echocardiographic diagnosis: PH unlikely** Tricuspid regurgitation velocity <=2.8 m/s, PA
systolic pressure <=36 mmHg, and no additional echocardiographic variables suggestive of PH I B

Echocardiographic diagnosis: PH possible

Tricuspid regurgitation velocity <=2.8 m/s, PA systolic pressure <=36 mmHg, but presence of
additional echocardiographic variables suggestive of PH class IIa level C

Tricuspid regurgitation velocity 2.9–3.4 m/s, PA systolic pressure 37–50 mmHg with/without
additional echocardiographic variables suggestive of PH class IIa level C

Echocardiographic diagnosis: PH likely

Tricuspid regurgitation velocity .3.4 m/s, PA systolic pressure .50 mmHg, with/without
additional echocardiographic variables suggestive of PH Class I level B

Exercise Doppler echocardiography is not recommended for screening of PH class III level C

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Abstract

BACKGROUND:

Pulmonary arterial hypertension is a rare disease with a poor prognosis. Globally, pulmonary vascular disease associated with congenital heart disease may represent the most preventable cause of pulmonary artery hypertension and its morbid and fatal squeals. Epidemiological data are scarce, particularly in the pediatric population of developing countries. This is the first description of the pediatric data in our setup too.

OBJECTIVES

To determine magnitude, common associated CHD ,co morbid conditions and treatment practices of patient with PAH with CHD age o to 18 years old children in TASH.

METHODS:

The study was retrospective chart review conducted from Jan 2011 to Dec 2012 with informed consent from research committee. Pediatrics patients aged 0-18 years with the diagnosis of CHD with moderate to large left to right shunt and others CHD that have potential to cause PAH were included. Patient characteristics, type CHD, type PAH, symptoms at presentation, duration symptoms before presentation, echo, x-ray, ECG, associated complication, co morbid condition, and treatments were among the most important data collected. Diagnosis was made with echocardiography in all the cases. Eisenmenger syndrome was defined when there was a reversed (pulmonary-to-systemic) or bidirectional shunt. The clinical characteristics between the patients with/without PAH and Eisenmenger syndrome were compared and their risk factors analyzed with a multivariate Logistic model, chi-square test and odd ratio.

RESULTS:

A total of 157 patients (78 male,79 female) was included in the study. Mean age at time of diagnosis CHD was 33 months (range 1 month-18 years) and mean at diagnosis of PAH was 40 months(range 1 month-12 years). PAH –CHD are diagnosed in 67(42.3) with fixed PAH being 33 (21%). Types of congenital heart diseases seen were VSD (26.8%), PDA (22.3%), ASD (6.4%), combined simple left to right shunt lesion (75.2%), tetralogy of Fallot (15.3%), D-TGA(5.7%), other complex congenital heart 3.8 per cent. Among the PAH-CHD patients, 49.2% of them had Eisenmenger syndrome. The patients with large shunts were at an elevated risk of PAH. Compared with isolated arterial septal defect ,ventricular septal defect and patent ductus arteriosus patients with multiple different defects are at increased risks of PAH (OR = 8.348,95%CI(3.34-20.13) $P < 0.004$) .Only 19(12.1%) patients had surgical or device for their

CHD. Overall 105(68.9%) have congenital heart disease that will require immediate intervention including cardiac catheterization and surgical intervention. 136(86.6%) and 23(14.6%) had one or more complication and co morbid conditions respectively at diagnosis. 77(49%) of the study subjects were on one or more forms of treatment for the associated complication. One (3%) of patient was on specific drug (Sildenafil) for PAH among those with fixed PAH. Death occurred in one patient during the study period.

CONCLUSION:

PAH(fixed) is a common (21%) complication in CHD patients in the clinic and ventricular septal defect is the most common pathogenic type of CHD. Patients with multiple types of defect are at increased risk of developing PAH. Patients with others complications(like CHF, recurrent chest infections) at presentations are at increased risk PAH. Nutritional deficiencies of different types are the common complication and/ or co morbidity identified. Only nineteen (12%) patients were operated for underling cardiac condition (CHD) and one patient is on specific drug for PAH.

I. Back ground

1.1 Introduction

The incidence of congenital heart disease is approximately 8 to 12 per 1,000 live births and appears to be constant around the world. The currently accepted paradigm for the development of pulmonary vascular disease associated with congenital heart disease maintains that increased pulmonary blood flow and pressure trigger unfavorable vascular remodeling. Endothelial cell dysfunction, abnormal shear stress, circumferential wall stretch, and an imbalance in vasoactive mediators conspire to promote vasoconstriction, inflammation, thrombosis, cell proliferation, impaired apoptosis, and fibrosis.[2]

Pulmonary hypertension associated with congenital heart disease is classified in category 1 PH, which includes also pulmonary arterial hypertension due to idiopathic (IPAH) and familial causes and related to or associated with other diseases, including connective tissue disease and HIV infection. [3]The rationale for inclusion of pulmonary artery hypertension associated with congenital heart disease in category 1 is the observation that the histology and endothelial cell abnormalities of category 1 pulmonary arterial hypertensive diseases are indistinguishable from each other. The plexiform lesion is the epitome of severe disease in all category 1 diseases. There may be differences at cellular, genetic, and molecular levels between disorders in category 1 that remain to be elucidated. For instance, Lee et al [4] have demonstrated that the plexiform lesions

of patients with familial pulmonary arterial hypertension contain monoclonal proliferating endothelial cells in contrast to the polyclonal endothelial cell proliferation in secondary pulmonary hypertension due to congenital cardiac shunts. Mutations in bone morphogenetic receptor protein receptor type 2 are less common in patients with pulmonary hypertensive congenital heart disease than idiopathic pulmonary hypertension, but when present might have a profound impact on outcome. [5,6]

Eisenmenger syndrome is the name given to the most severe spectrum of pulmonary vascular disease secondary to congenital shunt lesions. Although the disease bears the name of Victor Eisenmenger, [7] it was Paul Wood[8] who most elegantly characterized the disease in a masterly account that remains germane today. Wood defined Eisenmenger syndrome as pulmonary hypertension at the systemic level, due to high PVRI (800 dyne s/cm 5 or 10 WUm2) with reversed (ie, right-to-left) or bidirectional shunt. These patients have severely remodeled pulmonary vasculature and seldom respond to vasodilators with a large decline in PVRI, especially if the shunting is purely right to left. In general at this stage closure of the pulmonary-to-systemic connection is contraindicated and associated with a worse outcome than the natural history of Eisenmenger syndrome. [8]

Clinical presentation of patient with PAH-CHD depends on underling congenital heart disease and severity pulmonary hypertension. Symptoms related specifically to pulmonary hypertension result from the inability to increase pulmonary blood flow in response to physiologic stress. Other symptoms are caused by various multisystem complications associated with cyanotic congenital heart disease.Patients who develop Eisenmenger syndrome may be asymptomatic for long periods of time. The elevated pulmonary vascular resistance (PVR) prevents pulmonary overcirculation and the symptoms of heart failure. This can result in a delay in diagnosis. In the first weeks of life when the PVR begins to fall toward adult levels, an infant with a large atrial septal defect (ASD), ventricular septal defect (VSD), or patent ductus arteriosus (PDA) may present with congestive heart failure symptoms due to the large left-to-right shunt. This may simply be reflected by poor weight gain.[10]

Infants with the same defects who maintain a high PVR have less left-to-right intracardiac shunting and less pulmonary blood flow. Therefore, developing Eisenmenger physiology may remain undetected in infants with a high PVR and relatively large defects because they lack a

loud systolic murmur and/or diastolic rumble and the symptoms of heart failure. Patients may have a period of poor weight gain, reflecting congestive heart failure, that improves as pulmonary pressures increase and overcirculation decreases. Clues to the diagnosis may include only dyspnea upon exertion and exercise intolerance. These symptoms become increasingly evident with advancing age, particularly at adolescence, and may progress to lethargy and syncopal episodes[.10]

Erythrocytosis secondary to chronic cyanosis is an adaptation to low levels of circulating oxyhemoglobin and is present in most patients. Excessive polycythemia may result in hematocrit levels of greater than 65% and hyper viscosity syndrome. Hyper viscosity may lead to thrombo embolic events, cerebrovascular complications, gout, chest pain from pulmonary infarction, and hemoptysis. Most of the symptoms are nonspecific and are confirmed if they are relieved by phlebotomy. Any of the multitude of multisystem complications that occur in patients with congenital heart disease may be present.[10]

Examination findings vary with the progression of the disease. Early in life, infants with a large systemic-to-pulmonary communication may demonstrate mild pulmonary overcirculation with symptoms of corpulmonale. Initially, cyanosis is absent, and infants present with the signs and symptoms of heart failure. Physical examination may reveal tachypnea, nasal flaring, grunting, retractions, and tachycardia. An ausculatory examination may reveal a hyperactive precordium, systolic flow murmur, diastolic rumble, and hepatosplenomegaly. Cardiac examination findings are determined by the underlying anatomic defects. Delayed capillary refill may be present, indicating low cardiac output.[10]

As the PVR increases, the pulmonary circulation receives less blood flow, with gradually advancing pulmonary artery pressure. Symptoms of congestive heart failure wane. The right ventricle may become hypertrophied, and the chest,when examined, may be asymmetrical, with a right ventricular heave and a palpable P_2. As pulmonary resistance increases over time, a relative decrease in the left-to-right intracardiac shunting occurs, initially with periods of subclinical right-to-left and bidirectional shunting, followed by frank cyanosis, clubbing, and polycythemia (giving a ruddy appearance to the skin). [10]

A hallmark of Eisenmenger syndrome is this seemingly improved clinical condition, despite the lack of change in therapy for congestive heart failure. It represents a physiologically normalized condition caused by the progressively worsening pulmonary vascular obstructive disease (PVOD), with resolution of pulmonary over circulation and heart failure.[11]

Laboratory studies used in the diagnosis of Eisenmenger syndrome include complete blood count (CBC), biochemical profiles, and iron studies, in addition to blood gas assessments. Imaging studies can reveal cardiac structural defects and pulmonary changes, including irreversible alterations in the pulmonary system. Electrocardiography can also reveal signs of underlying

cardiac defect and of right ventricular hypertrophy, while histologic findings can be used to determine the stage of pulmonary vascular pathology.

In the early stages, chest radiography reveals a typical appearance of increased pulmonary flow with right ventricular or biventricular enlargement, right atrial or biatrial enlargement, pulmonary vascular plethora, and an enlarged main pulmonary artery. Advancing pulmonary vascular disease appears as a normal cardiac silhouette with dilated main and branch pulmonary arteries without evidence of pulmonary over circulation. In patients with severe pulmonary vascular disease, radiography reveals a normal-sized heart, pruning of the pulmonary vasculature (ie, diminished distal/peripheral pulmonary vascular marker), pulmonary infarction, and/or calcification of a patent dactus arteriosus (PDA). [10]Electrocardiographic findings are almost always abnormal in Eisenmenger syndrome. They include the following: Signs of right heart hypertrophy, in addition to abnormalities associated with the underlying defect, frontal plane QRS right axis deviation, tall monophasic R wave in V_1, deep S wave in V_6, ± ST and T wave abnormalities and P pulmonale[10]

The 6-minute walk test (6MWT), which requires minimal equipment and subspecialty experience, is simpler than the more formal and involved traditional cardiopulmonary exercise test (CPET). Moreover, the 6MWT is better tolerated in younger children, who often will not comply with the multiple leads, facemask, or other equipment needed for a CPET. The 6MWT may be effective in patients with a walk distance of less than 300 m. In patients above the 300-m threshold, however, a CPET should be considered.[12]

Two-dimensional (2-D) transthoracic imaging can reveal the particular features of the structural cardiac defect responsible for the shunt. Coexistent structural abnormalities can also be identified. Color-flow Doppler interrogation is useful for demonstrating the direction of intracardiac blood flow.[13]Pulsed and continuous wave Doppler measurements permit quantification of the intracardiac shunt, right ventricular pressures, and estimation of pulmonary artery systolic/diastolic and mean pressures by means of the modified Bernoulli equation[14] Other echocardiographic variables that might raise or reinforce suspicion of PH independently of tricuspid regurgitation velocity should always be considered. They include an increased velocity of pulmonary valve regurgitation and a short acceleration time of RV ejection into the PA. Increased dimensions of right heart chambers, abnormal shape and function of the interventricular septum, increased RV wall thickness, and dilated main PA are also suggestive of PH, but tend to occur later in the course of the disease.[1] Echocardiography can also be used to

identify surgical systemic-to-pulmonary shunts. Trans esophageal echocardiography is useful for imaging posterior structures, including the atria and pulmonary veins[.1,10]

Cardiac catheterization can be of value, after collecting clinical and noninvasive data, to confirm and/or demonstrate: Severity of PAH, conduit patency and pressure gradient, coexisting coronary artery anomalies (rare) and degree of shunting. Cardiac catheterization permits the examination of the intracardiac structure and exclusion of potentially reversible causes of pulmonary hypertension, as well as assessment of ventricular function (systolic and diastolic), examination of the intracardiac shunt, determination of pulmonary artery pressure and flow, and calculation of pulmonary vascular resistance (PVR).[11]

II) Literature review

Published reports estimate the incidence of congenital heart disease at eight to 12 per 1,000 live births. The incidence is similar in all countries and between races. In addition, in school-aged children the prevalence of the common congenital heart diseases is similar and also constant around the world. VSDs are the most common lesions, followed by ASDs and PDAs. These lesions affect the sexes equally and make up about 60% of all heart defects encountered in school aged children around the world; they appear to have remained constant over the last 30 years. [17] In less-privileged countries the prevalence in school-aged children is estimated at about 3/1,000 population.[18] This suggests significant infant attrition and/or incomplete case ascertainment. It was calculated that there are approximately 3.2 million children worldwide with an isolated ASD, VSD, or PDA who if untreated and surviving infancy would develop pulmonary vascular disease and suffer the crippling morbidity of hypoxemia due to shunt reversal and a shortened life expectancy.[17]

In the developed countries the prevalence of Eisenmenger syndrome due to simple lesions has decreased considerably. The Eisenmenger patient of the future is likely to have complex cardiac lesions. Therefore, pulmonary vascular disease associated with congenital heart disease is seen rarely in children in countries with privileged referral patterns, timely diagnosis, and surgical treatment. However; globally (80% of the population lives outside the developed countries), it is estimated that only 2% to 15% of patients with significant intracardiac or extracardiac shunt lesions receive curative intervention.[17] For example in Papua New Guinea by the time surgical therapy is offered 20% of a cohort of children will be inoperable because of advanced pulmonary vascular disease.[16]

One review of PAH-CHD in Sub- Sahara Africa shows prevalence of PAH-CHD is about 60% with Eiseimeger physiology being 11.2% at diagnosis and average age diagnosis being 17 months. In these studies 654 patients over 5years of admission: 272 (41.6%) had age < 24 months;127 pts had major complications of which 74 (11.2%) permanent cardiac or lung damage. Of the 471 children suitable for surgery: 207 operated (34 died, 15 denied).The same review shows in Mozambique the median age at diagnosis was 4 years (0-79), only 52.8% were diagnosed before the age of two, the commonest defects being L-R shunts (354;66%): VSD(32%), ASD(14%), AVSD(11%), PDA(9%) , PH is present in over 60% of patients & fixed pulmonary hypertension is the most common reason for contraindication to surgery and also in Nigeria fixed PAH is present in 11% of children with CHD at diagnosis.[19]

There for disease burden due to pulmonary vascular disease from inadequate treatment of young infants with congenital heart disease shares similarities in global epidemiology with all illnesses for which poverty and poor access to medical care are at the heart of the matter. A huge population of children with simple shunt lesions will die in childhood, adolescence, and young adulthood after a life characterized by recurrent illness and growth failure.[20] Which is in contrast between the 85% of babies born with congenital heart disease in the United States who are expected to reach adult hood and the mortality rate of 11% for all children 5 years of age in Papua New Guinea[21] and under five(5) mortality rate of 8.8% in our country according to EDHS of 2011.

The United Nations Children's Fund report in 2001 advised that timely intervention in the first 3 years of life is paramount in the approach to many childhood diseases and disabilities. Congenital heart disease should be included in this list if we are to prevent the associated pulmonary vascular disease in later life.[21] Standard recommendation for children with large left-to-right shunts or evidence of an elevated pulmonary vascular resistance is operative closure of the defect in the first 12 to 18 months of life. In patients predisposed to pulmonary vascular disease, such as trisomy 21, earlier repair by 6 months of age is recommended. Patients with truncus arteriosus or transposition of the great arteries with VSD are repaired within the first month of life. This strategy has been effective at reducing the development of Eisenmenger

syndrome. For instance, the 35- to 45-year survival in Finland after surgical VSD closure is 79%, after PDA ligation 88%, and after ASD closure 95%, in a country where 95% of the general population can expect to live 45 years. [22] In contrast, in Africa the mean age of referral of those children who do see a pediatric cardiologist is 17 months, and 5% to 10% of patients have Eisenmenger syndrome at referral.[20] In Sudan, only 15% of children who need an operation receive one. Even though the outcome for those operated ones is extremely good.[23] In Papua New Guinea, there is 21% mortality in those who need but do not receive an operation and, one presumes, a high rate of Eisenmenger syndrome.[16]

The prognosis of Eisenmenger syndrome is uniformly fatal; however, some patients survive into the sixth decade of life. The usual life expectancy of a patient with Eisenmenger syndrome is 20-50 years if the syndrome is diagnosed promptly and treated with vigilance. The onset of pulmonary hemorrhage is usually the hallmark of a rapid progression of the disease [24].The quality of life is poor in patients with Eisenmenger syndrome because exercise tolerance is extremely limited (due to limited oxygen uptake resulting from an inability to increase pulmonary blood flow) and complications are profound. Poor prognosis is predicted by syncope, elevated-right sided pressures, and hypoxemia. A study by Salehian et al reported that left ventricular dysfunction (defined as left ventricular ejection fraction [LVEF] < 50%), right ventricular hypertrophy, and signs and symptoms of heart failure predict mortality in patients with Eisenmenger syndrome. A simple echocardiograph score relying on right ventricular and right atrial characteristics was found to predict adverse outcomes in patients with Eisenmenger syndrome that is not associated with complex congenital heart disease.[25]

Although is not well known how other factors common in children with limited access to medical care might exacerbate the pulmonary vascular disease from congenital heart disease. Few studies for instance, in a group of children evaluated in Africa, 53% were anemic, 47% underweight, and 33% marasmic compared with a control group without congenital heart disease, of whom none were marasmic and 14% were underweight.[]TB is more than twice as common in patients with congenital heart disease, especially lesions with an increased pulmonary blood flow. TB may also mask the signs of congenital heart disease resulting in delayed referral for cardiac repair. [26]HIV infection is endemic in sub-Saharan Africa. Congenital heart disease affects 5% of children in Uganda with HIV compared with 2% to 3% in developed countries.[27] It is unknown how concomitant HIV infection or other infections such as malaria, which are more common in children with congenital heart disease, will promote or

potentiate pulmonary vascular disease due to congenital heart disease. [28] It is estimated that each year there are 100,000 new cases of congenital rubella syndrome. Up to 75% of those affected will have congenital cardiovascular malformations (60% will have a PDA). Despite maternal rubella infection can be almost eradicated by effective vaccination programs.[29]

Patients with Eisenmenger syndrome usually do not survive beyond the second or third decade. Long-term survival depends on the patient's age at the onset of pulmonary hypertension and the type of underling CHD. Data from a large case–control study of adult CHD patients matched with healthy individuals showed that median survival was greatly reduced in Eisenmenger's patients with complex cardiac defects compared with those with simple lesions. It illustrates, the presence of complex lesions in Eisenmenger's syndrome patients was associated with a survival reduction of 20 yrs, compared with patients with simple lesions; relative to subjects without Eisenmenger's syndrome, this represents a 40-yr reduction in survival.[30] Survival predominantly depends on right ventricular function. The mortality rate in pregnant patients with Eisenmenger syndrome is reported to be approximately 50%, although it may be higher. The most frequent terminal event in this syndrome is a combination of hypoxemia and arrhythmia in the setting of rapid increases in pulmonary vascular resistance or decreases in systemic vascular resistance (SVR). Death also commonly results from congestive heart failure, massive hemoptysis, or thromboembolism.[25]

The treatment of Eisenmenger syndrome varies widely and depends on the patient's age, degree of cyanosis, and subsequent polycythemia. Asymptomatic patients require periodic evaluation, with anticipation of potential complication.. All patients with intra cardiac right-to-left shunts have potential for the following: Syncope, paradoxical embolus, stroke, brain abscess, and sudden death , polycythemia, hemoptysis, and pulmonary infarction, congestive heart failure and endocarditis [10]

Behavioral modification and awareness of potential risk factors are critical to the management of patients with PAH-CHD. General measures include avoidance of strenuous exercise, although mild activity is beneficial, and prevention of dehydration. Patients with Eisenmenger's syndrome are at particular risk during anesthesia and surgery, and special care is required. Pregnancy is contraindicated in patients with Eisenmenger's syndrome as there is a high risk of maternal and fetal mortality; adequate contraception is, therefore, mandatory. Long-term supplemental oxygen therapy at home may improve symptoms. However, as this has not been shown to modify survival, at least when given only at night , the use of supplemental oxygen therapy is recommended only in cases in which it produces a consistent increase in arterial oxygen saturation and reduces symptoms[1,31].

The high incidence of pulmonary artery thrombosis (up to 20%) is associated with increasing age, biventricular dysfunction and dilatation of the pulmonary arteries. Given the lack of data, guidelines do not recommend the use of anticoagulants in PAH-CHD, but suggest they may be considered in patients with pulmonary artery thrombosis, signs of heart failure and absent or mild haemoptysis. Routine phlebotomy should not be performed as secondary erythrocytosis is beneficial for oxygen transport and delivery [32]. If moderate-to-severe symptoms of hyperviscosity are present, and iron deficiency and dehydration have been excluded, phlebotomy with isovolumic replacement should be performed carefully when the haematocrit is >65% . Iron deficiency has been shown to be associated with a higher risk of adverse outcomes (all-cause mortality, transplantation and hospitalisation due to cardiopulmonary causes) in Eisenmenger's syndrome patients and iron replacement therapy improves exercise tolerance and quality of life. There are no data to support the use of calcium channel blockers in patients with PAH-CHD and their use must be avoided. In particular, their use is contraindicated as this treatment class can result in an acute decrease in systemic arterial pressure and increase of the right-to-left shunt, which may lead to syncope and sudden death . Patients who present with significant haemoptysis should be considered for embolisation of relevant collateral vessels if appropriate [32]

Reflecting available data, current European Society of Cardiology guidelines focus on patients with Eisenmenger's syndrome and recommend that treatment with the endothelin receptor antagonist bosentan is initiated in Eisenmenger's syndrome patients in functional class III (class I, level of evidence B), with consideration being given to the use of other endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, prostanoids or combination therapy (class IIa, level of evidence C) [32]. This difference in recommendation level between bosentan and the other PAH-specific therapies occurs because only one randomised controlled trial of PAH-specific therapies has been conducted and this involved bosentan. The BREATHE-5 (Bosentan Randomized Trial of Endothelin Antagonist-5) trial and its long-term open-label extension study demonstrated the benefit of bosentan in patients with Eisenmenger's syndrome in terms of significant improvements in exercise capacity, haemodynamics and functional class compared with placebo, independently of the location of the septal defect [33]. Data from a number of studies have since confirmed these benefits in the longer term in patients with PAH-CHD and specifically in patients with Eisenmenger's syndrome. Importantly, treatment with bosentan has been shown not to reduce systemic arterial blood oxygen saturation over short- and long-term treatment, demonstrating that it had no negative effect on the overall shunt. Treatment with bosentan has also been shown to have a positive long-term effect on quality of life, a particularly important consideration for Eisenmenger's syndrome patients [34].

Despite the lack of randomized controlled trials for other PAH-specific therapies, data are available from small, open-label studies; the earliest showing treatment benefit with epoprostenol . Treatment with sildenafil has been shown to improve exercise capacity, Borg dyspnoea score, functional class, quality of life and haemodynamics in patients with PAH-CHD/Eisenmenger's syndrome and appears to be well tolerated [35], while a single study of ambrisentan suggests that this endothelin receptor antagonist may also be beneficial in this patient population. There is clearly an interest in using PAH-specific treatments in patients with PAH-CHD, but without further randomized controlled studies being initiated, evidence will continue to be based on single centre studies.[36]

Although potentially attractive, results from studies investigating the benefits of combination therapy using different classes of PAH-specific therapy in PAH-CHD are mixed. While some studies suggest that the addition of sildenafil to bosentan therapy may improve haemodynamics and exercise capacity, others have shown no benefit . However, overall, data suggest that treatment of PAH-CHD patients with PAH-specific therapy improves outcome. In a retrospective, single-centre analysis including 229 patients with Eisenmenger's syndrome, the use of PAH-specific therapies (advanced therapy: bosentan 73.5%; sildenafil 25%; epoprostenol 1.5%) was associated with a significantly lower rate of cumulative mortality over 7 yrs *versus* no therapy [36].

Significance of the Study

Despite high burden of problem in developing countries like ours there were no data that shows significance of PAH related to CHD. Therefore, this study is planned to report the burden of congenital heart disease-related pulmonary arterial hypertension among the under-privileged children with congenital heart disease attending follow-up clinic at a teaching referral hospital.

III. Objectives

3.1. General objective

To determine magnitude,common associated CHD ,co morbid conditions and treatment practices of patient with PAH with CHD age o to 18 years old children in TASH cardiac clinic from January 2011 to December 2012.

3.2. Specific objectives

To determine magnitude of PAH with CHD in TASH pediatric cardiac clinic.

To identify commonest CHDs associated with PAH and identified co morbid conditions.

To asses treatment practices, morbidity and mortality of patient with PAH with CHD

IV. Methods and Materials

4.1. Study Design study period

A cross-sectional retrospective chart review from January 2011- December2012.

4.2.Study population

4.2.1 Source population

Children with CHD attending pediatric cardiac clinic in Tukur Anbesa specialized Hospital (TASH) during the year 2011 to 2012.

4.2.2 .Specific /target populations

Inclusion criateria=All children with CHD, age 0 -18 year attended the clinic at least once-1) whose medical record are available and diagnoses of congenital heart diseases was made by echocardiography.

Exclusion criteria= 1) those with decreased pulmonary blood flow due to right out flow obstruction unless there is possibility of collaterals.2) patient with left side obstruction since it rare and need catheterization to diagnosis PAH. 3) Patient with restricted left to right shunt .4) children with Down's syndrome.

4.3. Sample size and sampling methods

In determining the sample size particular attention was given to getting adequate sample size that would ensure the generalization of the study findings. To effect this, the following assumptions and a standard sample size calculation formula is used to determine the number of CHD cases to be reviewed for the study.

Assumption: A relevant variable to the study under consideration i.e. the proportion of PAH(fixed) in CHD from a similar hospital based study X% or no similar study is identified, but study in some Africa was taken as base line, then P is (X% or10%). **Margin of error (d)** = 0.05 **With 95% confidence level** α = 0.05

Formula used to determine the sample size =

$N= (z\alpha/2)^2 * P (1-P) = (1.96)^2 * P (1-P)$

$d^2 \qquad (0.05)^2$

Based on the above assumption and using the following formula the sample size is calculated as:

$n= (z* \alpha/2)^2 * P(1-P)$

d

$n= (1.96)^2 * 0.10 (1-0.10)$

$(0.05)^2$

$n=3.8416 *0.25$

$.0025$

n= 138

To offset the high incomplete and ineligible rate[1] of the record card, 25% of the calculated sample size would be added to the final sample size figure. Thus, the final sample size was: calculated sample size + 25% of the calculated sample size

: 138 + 35

: 173

Sampling methods not used and all records of children with CHD, who were seen during the above time period, was reviewed to adequate numbers as there is no appropriate log book to get card numbers.

4 .4 Variables

4.4.1Dependent variables

Flow related PAH, Fixed PAH, Mortality and morbidity

4.4.2 Independent variable

Age , Sex ,Educational status of parents ,Address ,Types CHD ,age diagnosis, symptom at presentation , ECG,X-RAYS,ECHO finding ,Treatment modalities, Associated morbidities

5. Data collection Analysis

5.1Data Collection

The records of pediatric patients who had been assigned with the diagnosis of CHD to TASH cardiac clinic age 0 to 18 years, from January 2011 up to December 2012 were reviewed retrospectively. In order to get patients record, log book in the Pediatrics Cardiac clinic was accessed for card numbers. Having card numbers from the log-book, individual record was collected & reviewed using structured questioners by principal investigator trained medical professionals.

5.3 Data processing and analysis

Data was entered into SPSS for Windows, version 16 and analyzed. Descriptive statistics was displayed, as mean ± SD. Continuous variables will be tested for significance using t-test for single sample. Ordinal and categorical variables were tested using the Chi Square goodness-of-fit-test and multiple logistic regressions.

6. Ethical consideration

Ethical approval was taken from the Department of Pediatrics and Child Health review committee.

7. Limitations of the study

The biggest limitation of this study was the retrospective design - this is inevitably complicated by some incomplete data and lost records.

Total number of patients on follow up was not known thus difficult to use any sampling methods

Echocardiography is not gold standard diagnostic modality for PAH especially when TR was not present. Possible echo findings were not quantitative.

V) **RESULTS:**

A total of 157 patients (78 male,79 female) was included in the study. Most children were from Addis Ababa 98(63.7%),Oromia 32(20.3), Amhara and SNNR each 12(7.6%) and 1 patient from Tigray region.(table-1) Types of congenital heart diseases seen were VSD 42 (26.8%),35 PDA (22.3%), 10 ASD (6.4%), multiple simple left to right shunt lesion 31(21%), tetra logy of Fallot 24(15.3%), D-TGA(5.7%), other complex congenital heart 3.8 per cent(figure-1). Of 157 total 67(42.6%) patients were diagnosed with PH of which 33(21%) of were having fixed PAH. Mean age at time of diagnosis CHD was 33 months (range 1 month-18 years) and mean age at diagnosis of PAH was 40 months (range 05 months-12 years). Their average current age in months, patient's number, central values, and current age range for the patients with NPH, HPAH and FPAH were also compared: group I(NPAH) 90 patients aged months (1–216); group II(HPH), 34 patients aged months (5–180); group III(FPAH), 33 patients aged months (5–192).The mean age for the three groups were 64.78, 65.02 and 75.93.There was no significant difference between the first two, while mean age in group III was higher than in both of these (Table-4). Even though there seemed to be more males in group III and more females in group II&I (63.6 and 54%, respectively), there was no statistically established difference (p=0.07). There were 21 boys for 12 girls (63.4% and 36.6%, resp.) in group III. Duration of symptoms before of presentations varies from 01week to 132 months. Most patients(children) were symptomatic and 51% presented with symptoms of both heart failure(shortness of breath, sweating, cough, failure to thrive) and repeated chest infections(upper respiratory tract infection

and pneumonia) , 24.5% had symptoms pneumonia(cough, fever, fast breathing) ,12.5%cyanosis and others symptoms like syncope and cyanotic spells' were rare. Echocardiography was taken as main diagnostic imaging of the study both for CHD and PAH. Chamber size, presence of TR and PR, fiber shortening and ejection fraction were evaluated for each type CHD. All children had at least one chamber dilated with 80(51%) had left, 60(38.2) right and 17(10.8%) both chamber enlargement. Multiple logistic regression analysis was done for some echo findings and showed chamber diameters and size of CHD were found to have strong correlation with the outcome variable fixed PAH correcting for age at diagnosis and types of CHD. Table(4) Only 8(24.2%) and 2(6%) patients with fixed PAH had TR and PR respectively. CHD with isolated left to right classified as large 62(38.5%), moderate 58(36.8%) and with others complex CHDs were 37(23.3%). Almost all patients have normal ejection fraction. On chest x-ray 100(86%) patient had cardiomegally, 56(35.7%) increases vascularity and/or pneumonia and 24(15.3%) had normal findings. ECG was found for 95(60.5%) of the patients; among these 39(41%) had RVH/RVD with abnormal peaked P-wave, 10(10.5%) LVH/LVD, 10(10.5%) bilateral chamber hypertrophy/dilatation with p-mitralae and 36(37.8%) had normal ECG finding. Neither x-ray nor ECG finding showed significant association with PAH (table 2). Anthropometric abnormalities were important co morbidities with overall stunted 67.5%, underweight 36.9% and 25.4% severe wasting. 23(14.6%) of the children were found to have others co morbid and/or confounding factors other than nutritional deficiencies; six children had tuberculosis, ten had anemia, two children were have congenital rubella syndrome, and others (HIV,VACTERL association, hernia and ? De-Jorge's 'syndrome each one patient) at time of diagnosis. Of total 157 patients 136(86.6%) were having different types of complication due to CHD or/and associated PAH. Of these both recurrent chest infection (pneumonia) and CHF account for 54(34%), pneumonia alone 51(32.5%), CHF 17(10.8) polycythemia 15(9.6%) and others. All of the children with PAH (100%) had these complication at diagnosis table-5 .Of total(157); 42(26.8%) children were having more than two admit ion in six months for one or more of the above complications. There was only one death report in the sampled population during study period; 18 months old child diagnosed to have moderate VSD at the age of two months and admitted with CHF and pneumonia. Among study cases 19(12%) had got opportunity to have corrective surgery for underling CHD with only one child (3%) with persistent PAH after operation and others have minor complication that resolve after some time. Seventy seven (49%) of children were on different types of medical treatments. Of these children 56(72.7%)

were on anti -congestive drug like diuretic, spironolactone and digoxin. Only four (12%) children were started on selidenafil but three of them discontinued for unspecified reason at time study. (Table- 5)

Logistic regression analysis showed that patients with large shunts and patients with one or more different defects were at an elevated risk of PAH with (p=000,OR=8.34)respectively.(figure-2). Compared with atrial septal defect and patent duct us arteriosus patients with VSD were most frequent either isolated or in multiple defects were at increased risk of PAH (OR = 2.78, P < 0.04) .Patients with fixed PAH as compared to hyper kinetic PAH(HPH) has increased likelihoods of different complications at diagnosis (p=017 ,OR=,?)(Table-6).

Table-1 Socio-demographic characteristics of children with CHD at TASH during the year 2011-2012.

		Frequency	Percent	Cumulative Percent
Gender	Female	79	50.3	50.3
	Male	78	49.7	100.0
	Total	157	100.0	
Address	A.A	98	61.8	63.1
	OROMIA	32	20.4	84.1
	AMARA	12	7.6	91.7
	SNNR	12	7.6	99.4
	TIGRAY	1	.6	100.0
Educational status	Illiterate	8	13.5	13.5
	1to8	14	23	37.6
	9 to 10or12	9	15	51.7
	10+ or12+	29	48.3	100.0
	Total	60	100.0	

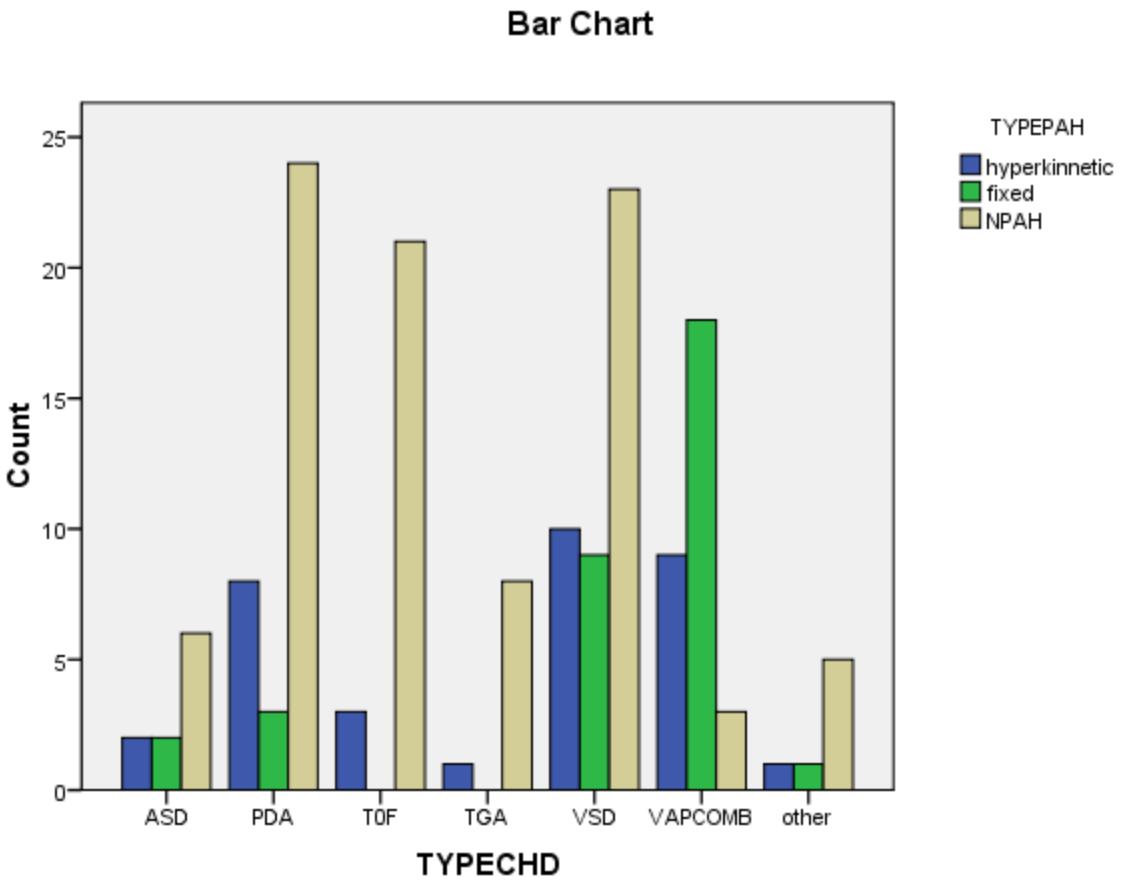

Figure -1 Bar graph show distribution of different groups patient with PH with in TYPES of CHD. VAPCOMB=Multiple shunt lesions ,NPAH-no PH.

Table-2 Frequency distributions of clinical presentation, x-ray, ECG ,ECHO finding of children with CHD at diagnosis at TASH during the year 2011-2012.

		Frequency	Valid Percent	Cumulative Percent
Clinical presentation	CYANOSIS	13	8.3	8.3
	SYPTOM OF CHEST INFECTION	38	24.2	32.5
	HEART FIALURE SYMPTOM	20	12.7	45.2
	SYPTOM OF BOTH	80	51.0	96.2
	Others	6	3.8	100.0
Nutritional status	Normal	51	32.5	32.5
	Stunted	8	5.1	37.6
	stunted &wasted	40	25.5	63.1
	Stunted&underwt	58	36.9	100.0
	Total	157	100.0	
ECG- findings	normal SR	36	22.9	22.9
	RVH orRVD	18	11.5	34.4
	LVH orLVD	10	6.4	40.8
	bilateral CD	3	1.9	42.7
	sinus tachycardia ,BICD and abnormal p-wave	7	4.5	47.1
	RCD AND ABNORMAL P - WAVE	21	13.4	60.5
	Total	157	100.0	100.0

Table-2 (Contous) Frequency distributions of clinical presentation, x-ray, ECG ,ECHO finding of children with CHD at diagnosis at TASH during the year 2011-2012

		Frequency	Valid Percent	Cumulative Percent
X-RAY	Normal	21	13.4	13.4
	Cardiomegaly	53	33.8	47.1
	Increased vascularity or pneumonia	13	8.3	55.4
	decreased vascular marking	3	1.9	57.3
	cardiomegally and increased vascularity	43	27.4	84.7
	cardiomegally and decreased vascularity	4	2.5	87.3
	NA	20	12.7	99.4
	Total	157	100.0	100.0
ECHO-FINDNG		Frequency	Valid Percent	Cumulative Percent
	TR PRESENT	17	10.8	10.8
	PR PRESENT	6	3.8	14.6
	BOHTH PRESENT	1	.6	15.3
	BOTH NOT PRES	133	84.7	100.0
	Total	157	100.0	
Size CHD	Large	62	39.5	39.5
	Moderate	58	36.9	76.4
	Unclassified	37	23.6	100.0
	Total	157	100.0	
Chamber size	RHCD	60	38.2	38.2
	LHCD	80	51.0	89.2
	BOTH	17	10.8	100.0
	Total	157	100.0	

Table 3 shows mean,std.deviation and ranges of different chamber size variations in mm between patients with NPH , HPAH and PAH after corrected to age.

TYPPAH2		PA	LV	LA	RV	RA
NPH	Mean	16.1159	30.8553	21.1711	16.1622	20.3867
	N	69	76	76	74	75
	Std. Deviation	5.20050	9.20826	5.61994	5.40174	6.90846
	Minimum	6.00	12.00	12.00	9.00	11.00
	Maximum	28.00	57.00	38.00	31.00	40.00
PAH	Mean	21.5600	32.6154	24.8846	20.6923	25.7308
	N	25	26	26	26	26
	Std. Deviation	6.18520	1.00163E1	8.35860	6.96718	8.58630
	Minimum	10.00	13.00	11.00	10.00	10.00
	Maximum	32.00	54.00	44.00	38.00	40.00
HPH	Mean	20.2593	36.5357	26.3929	18.3333	23.4444
	N	27	28	28	27	27
	Std. Deviation	4.48581	1.00719E1	8.03852	7.64098	8.44135
	Minimum	13.00	19.00	11.00	11.00	13.00
	Maximum	28.00	57.00	47.00	45.00	47.00
Total	Mean	18.1653	32.4308	23.0385	17.5512	22.1172
	N	121	130	130	127	128
	Std. Deviation	5.75666	9.75191	7.11413	6.47181	7.85661
	Minimum	6.00	12.00	11.00	9.00	10.00
	Maximum	32.00	57.00	47.00	45.00	47.00

NPH= no PH,PAH =fixed PH, HPH=hyper dynamic PH

Table-4 The mean distribution of symptoms duration, time echo last taken , age at first **symptom, age at diagnosis CHD ,age at diagnosis of PAH and duration of follow up children** with CHD at TAS Hospital during the year 2011-2012

	N	Range	Minimum	Maximum	Mean	Std. Deviation	Variance
Symptom duration	154	132.00	.00	132.00	11.2175	21.04585	442.928
Time EHO last taken	157	135.00	1.00	136.00	20.2166	21.02206	441.927
Age at frist symptom	157	144.00	.00	144.00	22.5796	36.16821	1.308E3
DURATION OF FOLLOUP	157	197.75	.25	198.00	34.6385	34.80173	1.211E3
AGE AT DIAGNOSIS PAH	66	155.00	1.00	156.00	41.2879	42.42850	1.800E3
AGE AT REPAIR	20	150.00	6.00	156.00	51.5000	46.56687	2.168E3
CURENT AGE	157	215.00	1.00	216.00	67.2357	50.13842	2.514E3

Table 5 Distribution of complication, co morbid conditions and treatment practices of under 18 years children with CHD at THSH cardiac clinic follow up during the year 2011-2012

		Frequency	Valid Percent	Cumulative Percent
complications	Not reported	16	10.2	10.2
	POLYCYTHEMIA	15	9.6	19.7
	CHF	17	10.8	30.6
	RECCURENT PNEUMONIA	51	32.5	63.1
	OTHERS	4	2.5	65.6
	CHF &CHEST INFECTIONS	54	34.4	100.0
	Total	157	100.0	
comorbidity	Not reported	134	85.4	85.4
	Tuberculosis	6	3.8	89.2
	HIV	1	.6	89.8
	Anemia	7	4.5	94.3
	Rubella	2	1.3	95.5
	Others	7	4.5	100.0
	Total	157	100.0	
TRx types	Not reported	80	51.0	51.0
	Anti-congestives	56	35.7	87.3
	Selidenafile	4	2.5	89.8
	Anti-coagulants	2	1.3	91.1
	Others(heam-up, phlebotomy…)	14	9.6	99.4
	Total	157	100.0	100.0

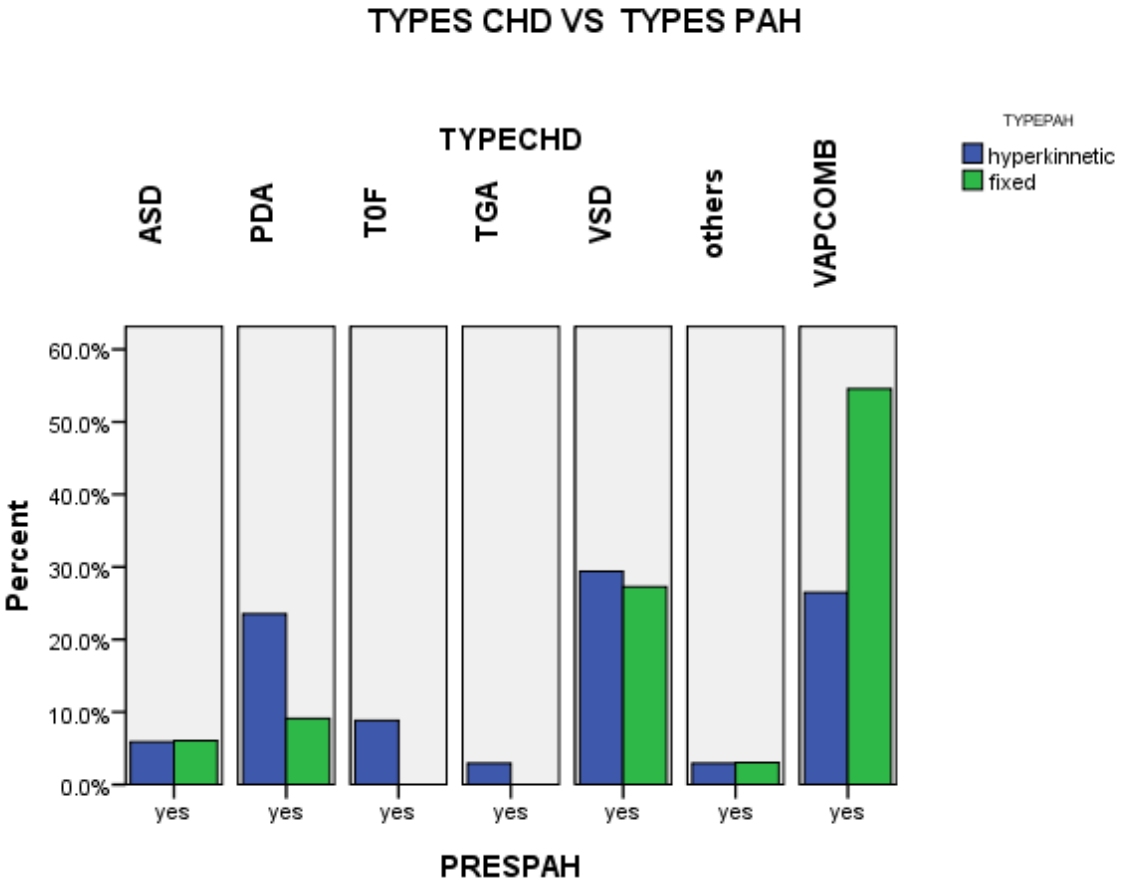

Figure 2 Children with multiples shunt lesion(PAVCOM) shows significant assosations fixed PAH,P=0.000 &OR=8.348 with 95% CI(3.465-20.138) when compared HPH.

.PRESPAH=Presences of PAH

Table-6 cross-tabulation of some variables vs out come variable (fixed PAH)

		fixed	PAH	Total	p-value& OR &95%CI
		yes	no		
GENDER	female	12	67	79	0.07
	male	21	57	78	
Total		33	124	157	
Family history	Yes	4	3	7	0.016,5.956(1.439-6.071)
	No	29	121	150	
COMRBIDTY	Yes	4	19	23	
	No	29	105	134	
Total		33	124	157	0.26
Repair CHD	Yes	1	18	19	
	No	32	106	138	
Total		33	124	157	
RECCURENTADMITION	YES	14	28	42	0.022,2.526
	NO	19	96	115	(1.115-5.652)
Total		33	124	157	
COMPLICATIONATDIAGNOSIS	No	4	0	4	
	Yes	30	33	63	0.001 0R=?all had com.
	Total	34	33	67	

VI Discussion

Correct management of heart defects with left-to-right shunt is important in the prevention of progressive pulmonary vascular disease. It is estimated that pulmonary vascular disease develops in 15% (10–18%) of all CHD. The uncorrected CHD defects especially in a left-to-right shunt; the resulting continual increase in pulmonary flow increases tensile stress, which leads to an elevation of pulmonary resistance (Rp) and finally to pulmonary vascular damage [1]. In the initial stage of CHD with left-to-right shunt, PAP increases due to the higher pulmonary flow (Qp) that follows the fall in Rp during the postnatal period. This is the stage of hyperkinetic PH, caused only by increased flow in the presence of low Rp indexes. The structural changes resulting from the long-term tensile stress due to increased flow in the pulmonary vascular bed are luminal narrowing and the consequent resistance increase. Irreversible change takes place in the advanced stages of this process [1].

In our review, the average age of the patients who developed PAH and PH was, respectively,65.9 and 75.4 months. A predominance of boys, with 63.7%, was observed among PAH patients in our study, not consistent with the published literature which is more in favor of female [1].The estimated prevalence, in developed countries, of PAH in adults with CHD including a left-to-right shunt is 1.6–12.5 cases per million [2]. According to data of the Dutch CONCOR National Registry, PAH develops in 6.1% of cases with septal defect [2]. No information is available on the incidence or prevalence of PAH accompanying CHD in children. The frequency of PAH in our patients with septal defect and some cyanotic and non cyanotic CHD was 33 in 157 (21%).This higher than expected proportion of similar study in Africa may have been due to the inclusion of patients with moderate to large defects, late age at diagnosis of CHD and only n=19(12.1%) patients had opportunity to under gone corrective surgery despite 34.64 +/-34.8 months mean and std.of follow up duration [17]. The size and location of the septal defect are an important determinant of PAH in the presence of CHD both in children and adults. Simple defects are considered in two groups according to location, pre tricuspid and post tricuspid shunts [2]. Pre tricuspid lesions (ASD) are associated with a later onset and a lower-frequency PAH in response to the increase in pulmonary circulation compared to the post tricuspid shunts (VSD, PDA). Post tricuspid shunts, VSD and PDA, lead to both pressure and volume overload. Defect size is of importance equal to that of location. Patients with large defects are more prone to development of PAH than those with smaller ones. PAH develops in only 3% of small and

middle-sized VSD, while it reaches up to 50% in frequency with large defects [6]. Small defects are defined as <1 cm for VSD and <2 cm for ASD [1] Per membranous VSD 9 and18 isolated and in combination respectively was the most frequently found condition, in 27 of 33 patients (81.1%) who developed PAH in our study. PAH was found in two patients with either secundum ASD. Thus, according to our study the condition with the highest risk of developing PAH is peri membranous VSD specially when presents as multiple lesion. Patients with the latter condition should be closely followed up and treated early. PDA was second in frequency with 3 of 33 patients with PAH (12%) and it was most frequent condition in patients with multiple lesions with VSD. Studies in a groups of children evaluated in Sub Sahara Africa, 53% were anemic, 47% underweight, and 33% marusmic compared with a control group without congenital heart disease, of whom none were marusmic and 14% were underweight; TB is more than twice as common in patients with CHD and TB may also mask the signs of congenital heart disease resulting in delayed referral for cardiac repair. [26] Congenital heart disease affects 5% of children in Uganda with HIV compared with 2% to 3% in developed countries.[27]Comparable to these in our study 67.5% of children were stunted, 36.9% under wt and 25.4% were marusmic at time of diagnosis CHD. Anemia is reported only 6%. 19(12,1%) of 157 patients were operated with only one patient with persisting PAH. This is nearly a similar case in Sudan where 15% under gone surgery of those who need it but minor complications postoperatively to 8%. Twenty one 66.7% of children with PAHs are on lasics and spironolactone that may require precautions due to high risks of hyper viscosity and need for preload these patients. Only one patient was on specific treatment for PAH like selidanafil. This is as opposed to current recommendations for treatments of PAH.(1,36)

VII)Conclusions and recommendations

In conclusion prevalence of PAH is higher than study at similar setups. Higher average age at diagnosis of CHD in our patients may need due attentions. Patient with a diagnosis of VSD and multiple defects are the most at risk for PAH among those with large left-to-right shunt. Most children have complication other than PAH. Malnutrition is a commonest co morbid condition identified and those children may need close follow up and treatment. Only one patient is on specific drug for PAH. 66.7% of patients with right to left shunt or bidirectional shunt (PAH) have been on diuretics and spironolactone which need precaution as these can cause series complication. This study recommends the hospital management and others responsible bodies to salvage these children before they develop this fatal and progressive disease. At last but not the least the clinic needs logbook for registration; that contain columns of at least types of CHD, size of defect, known or ? Syndromes, year at start of follow up in addition to age, address, patients card number and if possible parents phone number to solve problem to access patients chart and get adequate information's.

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Annex

VIII. Questioner for review of prevalence of PAH-CHD in TASH under 18 years old children cardiac follow up clinic during the year 2011-2012

1. *Name……*
2. *Age…… sex……*
3. *Address of child (place of residence)……..*
4. *Family education status*
5. *Mother a)<4th grade b) 4-8 c) 8-12 d) >10th or 12th*
6. *Father a)<4th grade b) 4-8 c) 8-12 d) >10th or 12th*
7. *Durations of symptoms before presentation……age at first symptoms……..*
8. *Main complaint during this time(at presentation)*
    a) *dyspnea b)cyanosis c)syncope d) recurrent infections e)failure to thrive f)heart failure symptoms*
    b) *NYHA / Ross function class-*

        a)class- I b) class-II c) class-III d) class-IV
9. *Age at diagnosis of CHD……*
10. *Type of CHD……*
11. *Age at diagnoses of PAH with echocardiography……*
12. *Types of PAH-CHD at diagnosis considered*

        a) Hyperkinetic PAH…. b) Fixed PAH……..

13. *when was echo taken last?.....*
14. *what were echo finding at diagnose*
    a. *RA size for body wieght……*
    b. *RV size for body wieght ……*
    c. *LA size for body wieght ……*
    d. *LV size for body wieght ……*

e. *PA size for body wieght ……*
f. *TR Jet gradiet(if present)……*
g. *PR a) present……..b) absent……*
h. *Ejection fraction……*
i. *Fiber shortening……*
j. *RV/PA if estimated……*
k. *Ps/Qs if cath-was done……*

15.What are X-RAY finding if available at diagnoses
……
……
……..
16.What are EKG finding if available at diagnosis
……
……
……
……
17.Was CHD repaired a) yes b) no
18.If yes for above question, what was-
a)age at repair……
b) specify any complications after surgary ……
19.Is there family history of the same illiness? a) yes b) no
2o.Is there any comorbid conditions ?a) yes b)no
21.If yes what are these ?
a)OSA(due to ATH other condition)
b) pulmonary problem(interstitial lung disease,BPD,….
c) others specify(Tuberculosis,HIV ,anemia, malaria…..)
22.if there was anemia for Q No 21 what are the RBC indices?.....
23.Was there any complication at diagnosis; a) yes b) NO
24.IF yes for 22 , what are these complications?
a) *failure to thrive b)polycythemia c)CHF d) arrhythmia e) stroke f) infective endocarditis g) recurrent chest infection h)others*

specify……

……

25.Was the child on any form treatment? A) yes B) no

26.If yes, for the above questions,what are these treatment options?

A) oxygen therapy

B) anti congestive drugs- digoxin ,lasix,spironolactone…

C) specific drug for PAH like;(sildenafil .....)

d) anticoagulant (warfarin ,subcutaneous heparin)

E) others if any specify

27.If yes for how long is the child on treatment?

a)o-6 b)6-12 c)12months -3yrs d)>=3yrs

28.Was he/she having repeated admission? a) yes b) no

29.If yes for Q 28 what were reasons for admission specify?.....