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REVIEW ARTICLE

Eisenmenger Syndrome: A Revisit of a Hidden but Catastrophic Disease

Le Syndrome d'Eisenmenger : Un Réexamen d'une Maladie Cachée Mais Catastrophique

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ABSTRACT

BACKGROUND: Eisenmenger syndrome (ES) is a rare condition seen in children with congenital heart disease (CHD). It is characterized by raised pulmonary vascular resistance (PVR) arising from a shunt reversal with the presence of desaturated blood in the systemic circulation. Proper timing and early intervention in children with congenital heart disease have made the syndrome a rare occurrence. However, this cannot be said in developing countries where facilities for the diagnosis and management of children with congenital heart disease are not optimal.

OBJECTIVES: The aim of this narrative review is to highlight the importance of early diagnosis and to review the new techniques in the evaluation of children with ES. It also highlights in a snapshot the state of management of ES in a developing country.

METHODS: A search for published data on ES was done through several search engines such as Pubmed, google scholar citation, systematic reviews, and meta-analysis. This involves research done over the past 30 years. Keywords such as Eisenmenger'syndrome, 'congenital heart defect', 'Pulmonary hypertension','catherterization', 'echocardiography', and 'children' were used.

RESULTS: This review shows the new technique in the diagnosis, aetio-pathogenesis, management and treatment of children with ES in-depth descriptive analysis and new advances in the management of children with ES.

CONCLUSION: Eisenmenger syndrome is a preventable disease that can be curbed by early diagnosis and treatment of children with congenital heart disease, especially in the developing world. **WAJM 2023; 40(9): 973–981.**

Keywords: Eisenmenger syndrome; Children; Congenital heart disease; Pulmonary hypertension; Management.

RÉSUMÉ

CONTEXTE: Le syndrome d'Eisenmenger (SE) est une affection rare observée chez les enfants atteints de cardiopathie congénitale. Il se caractérise par une augmentation de la résistance vasculaire pulmonaire (RVP) due à l'inversion d'un shunt et à la présence de sang désaturé dans la circulation systémique. Le syndrome est devenu rare chez les enfants atteints de cardiopathie congénitale grâce à un choix judicieux du moment et à une intervention précoce. Toutefois, il n'en va pas de même dans les pays en développement où les moyens de diagnostic et de prise en charge des enfants atteints de cardiopathies congénitales ne sont pas optimaux.

OBJECTIFS: L'objectif de cette revue narrative est de souligner l'importance d'un diagnostic précoce et de passer en revue les nouvelles techniques d'évaluation des enfants atteints de SE. Elle met également en lumière, sous forme d'un instantané, l'état de la prise en charge de l'ES dans un pays en développement.

MÉTHODES: Une recherche de données publiées sur l'ES a été effectuée à l'aide de plusieurs moteurs de recherche tels que Pubmed, google scholar citation, revues systématiques et méta-analyses. Il s'agit de recherches effectuées au cours des 30 dernières années. Des mots clés tels que "syndrome d'Eisenmenger", "malformation cardiaque congénitale", "hypertension pulmonaire", "cathétérisme", "échocardiographie" et "enfants" ont été utilisés.

RÉSULTATS: Cette revue présente les nouvelles techniques de diagnostic, d'étio-pathogénie, de prise en charge et de traitement des enfants atteints de SE, ainsi qu'une analyse descriptive approfondie et les nouvelles avancées dans la prise en charge des enfants atteints de SE.

CONCLUSION: Le syndrome d'Eisenmenger est une maladie évitable qui peut être enrayée par un diagnostic et un traitement précoces des enfants atteints de cardiopathies congénitales, en particulier dans les pays en développement. **WAJM 2023; 40(9): 973–981.**

Mots-clés: Syndrome d'Eisenmenger; Enfants; Cardiopathie congénitale; Hhypertension pulmonaire; Prise en charge.

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INTRODUCTION

Eisenmenger syndrome (ES) is defined as a group of symptoms that arose from surgically uncorrected congenital cardiac defect with resultant shunt reversal, attendant cyanosis, and pulmonary hypertension.[1–3] Hitherto, the left to right shunt lesion over time is converted to a right-to-left shunt due to persistent perturbation of the pulmonary endothelial lining and associated increased vascular resistance.[1,2] Eisenmenger syndrome was first reported in 1897 by Victor Eisenmenger, an Austrian Physician. He described the history and postmortem details of 32 – a year-old man with VSD and cyanosis.[2–5] It was in 1958 in Paul Wood's Croonian Lectures that the term "Eisenmenger Syndrome was coined.

ES describes the gradual process of development of Pulmonary Hypertension (PH) and Pulmonary vascular disease (PVD) in large left to right shunt lesions leading to bidirectional or reversed shunt. It prevents the natural process of lowering the pulmonary vascular resistance (PVR) after birth to normal. ES is a late complication of an uncorrected left to right shunt.[2–4] Clinical manifestations include chronic hypoxia with exercise intolerance and right heart failure.[2–4]

The prevalence was 8% of the first 1000 cases of congenital heart disease (CHD) in Wood's series (ref). However, it has decreased to 4% in recent studies due to early detection and treatment; via echocardiography, interventional and surgical correction of CHD.[2-4] There are reports that the management of ES with drugs has some beneficial effects.[2] However, local experience and additional cases are necessary to further confirm its efficacy.

Proper timing and early intervention in children with congenital heart disease have made the syndrome a rare occurrence.[2] However, this cannot be said in developing countries like ours where facilities for the diagnosis and management of children with congenital heart disease are not optimal.[2] The review article describes Eisenmenger syndrome (ES) as a rare condition seen in children with congenital heart disease (CHD). This narrative review is aimed at highlighting the prevalence, aetiopathogenesis and current trends in the management of ES. This work also harnesses the management of ES in a developing country like Nigeria.[2]

METHODS

Keywords – 'Eisenmenger' syndrome, 'congenital heart defect', 'Pulmonary hypertension' 'catherterization', 'echocardiography', and 'children' were searched in PubMed database and Google Scholar citations for studies, which were published within the past 30 years. The Cochrane Database of Systematic Reviews, meta-analysis, and some textbooks published within the same period were included in the descriptive review.

Historical Perspectives

This syndrome was described in 1897, by Victor Eisenmenger, an Austrian Physician. He noted features of hemoptysis in a child who earlier had symptoms of breathlessness and bluish discoloration of the body at infancy.[4] He described the history and postmortem details of a 32 – year-old man with a large Ventricular Septal Defect (VSD) and cyanosis.[2–5] It was in 1958 in Paul Wood's Croonian Lectures that the term "Eisenmenger Syndrome was coined. Two decades later, Maude[5] documented an overriding of the aorta in a child with VSD and noted distinct characteristics between the aortic overriding, a simple VSD and the, Teratology of Fallot (TOF). He coined this phenomenon "the Eisenmenger Complex." Eisenmenger Complex (EC) is different from ES, and is defined as cyanosis in children with congenital heart disease which include ventricular septal defect, overriding of the aorta and dilatation of the pulmonary vessels with no pulmonary stenosis.[5]

Epidemiology

Hjortshoj *et al*[6] has documented the prevalence of ES as having decreased to 9% from 1977 to 2012. Their reportage showed a median survival rate of 38.4 years. In Nigeria, Buba[7] *et al,* had documented the prevalence of 6.8% cases of Eisenmenger syndrome which included cases of Atrio- ventricular canal defect, Ventricular septal defect, atrial septal defect and Ebstein's anomaly. It occurs at an earlier age, with a turbulent course in children with Down syndrome. The frequency of Down syndrome in children with ES was 13% in one series. The occurrence of early and progressive pulmonary vascular resistance and pulmonary hypertension in children with Down syndrome has long been elicited. Due to new innovations in medicine, the age at death has increased from about 28 years to 46 years over the past 3 decades in the general population.[7]

The Euro Heart Survey has shown that ES was present in 5.7% of 4110 adults while the Nationwide Registry of adults with congenital heart defects in the Netherlands has documented ES accounting for 1% of the 5970 registered patients. This study is similar to that obtained by Buba *et al*[7] despite the fact that the latter used a smaller sample size. Of the 1824 patients with either pre-tricuspid or post-tricuspid shunt lesions, 8% of them were known to present with ES.[7]

Besides, Erwin[8] *et al* has reported a prevalence of 17% in 727 subjects with congenital heart disease.[8] Eisenmenger syndrome occurs mostly in children with complete atrioventricular canal defect, Atrial septal defect (ASD) of the primum variety(43%), and Ventricular septal defect (16%), patent ductus arteriosus (16%), and Ostium Secundum atrial septal defect (6%). The level, size, severity and velocity of flow are determinants of ES. It is noted that ES occurs in 53% of children with a post-tricuspid shunt and 9% of children with a pre-tricuspid shunt.[8] Age of onset.

Danieleto *et al*[9] in his reportage noted that Eisenmenger syndrome usually develops before puberty, however, studies of onset in adolescence and early adulthood have been reported in their study. Kaemmerer *et al*[10] noted that the age of presentation depends on the severity of disease. They noted that patients with ES may die between the third decade and fourth decade of life 30 and 35 years. However, survival to late adulthood has been reported.[11] Children with a very large PDA may develop ES by age 4–7 years.[12] Guo *et al* noted that children between the ages of 15 and 18 years had the highest prevalence of

Eisenmenger syndrome. They documented age prevalence of 11.5% in the reportage.

Gender Predilection

Most studies have shown that ES affects both male and females equally with no racial predilection.[12]

Frequencies for various Cardiac Lesions

Kidd *et al*[13] noted that about 3% of patients with VSD of size less than ≤1.5 cm and 50% of patients with VSD of size more than 1.5cm develop Eisenmenger's syndrome.[14] Guo[23] *et al* noted that Eisenmenger syndrome occurs in 1.8% in VSD patients, 0.0% in ASD patients, and 0.9% in PDA patients.

Aetio-Pathogenesis/Clinical Features

Using Ohms law, flow (Q) is directly proportional to pressure and inversely proportional to resistance Q = P/R.[9] Any increase in flow, as seen in children with intra-cardiac defects with prior left-to-right shunts, results in increased pulmonary artery pressures and attendant vascular injury which is irreversible. Figure 1.

Due to increase vascular resistance seen up-till 8-12 weeks of age, Pulmonary vascular damage right to left shunt poses no threat prenatally.[9] This can be explained by the fact that the increased PVR of the fetus limits left-to-right shunting. Due to the shift from fetal to adult circulation, the pulmonary vascular resistance decreases with an increase right ventricular compliance and fall in right ventricular pressure with resultant left-to-right shunt and increase in pulmonary blood flow. However, over time, the continuous pulmonary flow leads to continuous perturbation of endothelial lining, neo-vascularization and attempts at healing with organization.[10] These abnormalities are triggered by mediators such as endothelin-1, intrinsic elastase, vascular endothelial growth factors, thromboxane and activated platelet.[11–14] With time, and without intervention, pulmonary vascular resistance increases with shunt reversal.

Though these changes are common with simple congenital heart defects with left to right shunt lesion, increased pulmonary vascular disease can also develop in children with complex cyanotic congenital heart diseases associated with increased pulmonary blood flow. It is pertinent to note that cyanosis which is seen in such complex cardiac lesions, tends to get worse and hastens the development of ES. For instance, children with congenitally corrected transposition of the great artery (ccTGA), transposition of the great artery (d-TGA) and Tuncus arteriosus can develop the pulmonary vascular disease within the first year of life if not surgically corrected.[10]

Children with ES usually present with exercise intolerance, breathlessness on exertion and worsening cardiac output due to increase right-to-left shunt. There is an attendant defect in stroke volume and heart rate which could result in weakness, dyspnoea, dizziness, or sudden death during exercise or severe exertion. With imminent right ventricular diastolic dysfunction and impaired relaxation, symptoms of right-sided heart failure become evidenced especially in older children and adolescents. Persistent cyanosis activates the oxygen haemoglobin curve and shifts it to the right. polycythemia occurs and, if severe can lead to symptoms of hyper-viscosity such as blurring of vision, throbbing headache and vomiting. Brain abscess, hemoptysis, systemic embolus and cerebrovascular accident could occur from persistence right-to-left shunt.[10]

Physical examination of the child with ES will reveal a child in obvious respiratory distress as evidenced by the flaring of the ala-nasi, intercostal and subcostal recessions with trachea tug at times and grunting respiration.[10] The pulse may be bounding or rapid with tachycardia, there is increased jugular venous pressure, hyperactive precordium, and heaving of the lower- left sternal border suggesting right ventricular hypertrophy. There may be a heaving apex if there is compensatory left ventricular hypertrophy.[10] The pulmonary component (p2) of the second heart sound is loud with a splitting of the second heart sound suggesting pulmonary hypertension. With the advancement of pulmonary hypertension, the previous murmur in a child with a left to right shunt diminishes, S2 is single (an aortic component of the second heart sound is only heard), and a systolic ejection click from a dilated

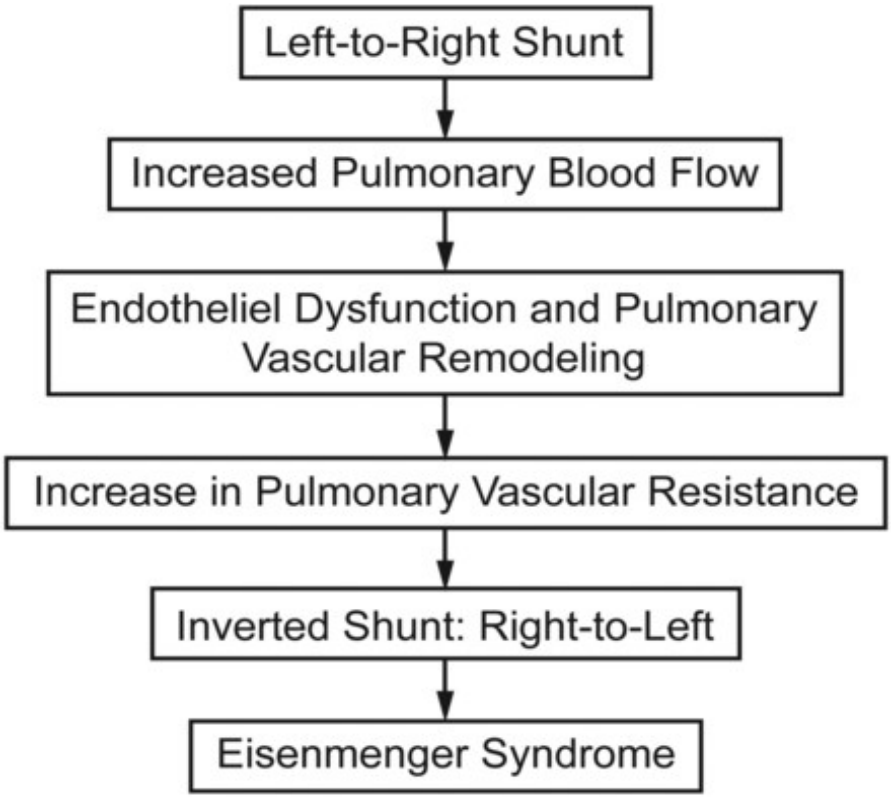

Fig. 1: Diagnosis of Pulmonary Arterial Hypertension from ES[15].

pulmonary artery may also be elicited. Besides, two different qualities and types of murmurs may be heard due to the after-effect of the pulmonary hypertension.[10] The first is the diastolic murmur heard at the second left intercostal space, this is the murmur of pulmonary regurgitation, secondly, a systolic murmur of tricuspid regurgitation is noted at the tricuspid area. Right ventricular failure may produce symptoms of elevated jugular venous pressure, gallop rhythm, hepatomegaly, and peripheral edema.[11]

Natural History

The size of the shunt defect is crucial in determining the course of ES in children with congenital heart defects. For instance, about 3% of children with a small ventricular septal defect (VSD) and 50% of children with a large VSD can develop ES.[15] The onset of ES occurs earlier in children with VSD or patent ductus arteriosus (PDA), and at adulthood in children with atrial septal defect (ASD). Death occurs between the ages of 30 and 35 years.[15,16] Children with ES present with a much better natural history than those with primary pulmonary hypertension. For instance, it is noted that 54% of subjects with VSD who had ES are still alive 20 years after diagnosis of ES.[17] It is noteworthy that the shunt defect in a child with ES need not be closed once the irreversible pulmonary vascular disease is established. This is because these defects now act as a puff-off valves and help to maintain systemic cardiac output in the course of a sudden increase in pulmonary vascular resistance. Maternal mortality of 45% has been reported in mothers who had ES.[18] Besides, other extra-cardiac surgical interventions increase mortality by about 19%. Non-cardiac-related surgeries should be performed in an intensive care unit with well trained and highly specialized cardiac anesthetists.[18]

Certain factors such as increased pulmonary arterial pressure increased pulmonary blood flow, and the presence of hypoxia or hypercapnia play vital roles in the clinico-pathogenesis of ES.[18]

It is noted that adults with ES may have a better prognosis compared to those with other causes of idiopathic pulmonary hypertension.[19,20] Eisenmenger syndrome worsens the natural history of children who had prior elevated pulmonary venous pressure from mitral stenosis, left ventricular dysfunction, and restrictive cardiomyopathy.

Investigations

Certain investigations will be of benefit in the diagnosis of children with Eisenmenger syndrome. This will also help in the management of the disease.

Chest Radiograph

Chest X-ray reveals pulmonary plethora (increase pulmonary flow) in the early stage of ES.[21–24] There is right ventricular preponderance and both ventricles may be enlarged with attendant right atrial and/or bi-atrial enlargement with dilatation of the main pulmonary artery. In a prolonged disease, the branch pulmonary arteries are dilated but the cardiac silhouette remains normal without pulmonary plethora.[24] However, in severe pulmonary disease, there is normal cardiac size, with diminished (pruning of the pulmonary vessels) vascular fields. (Figure 2) in children with ES who had PDA as the cause of the ES, there could be infarction with or without calcification.[24]

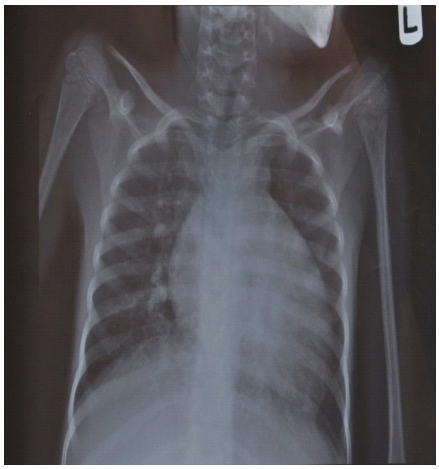

Fig. 2: Showing with diminished (Pruning of the Pulmonary Vessels) Vascular Fields.

Electrocardiogram (ECG)

Children with Eisenmenger's syndrome may show the following findings on ECG.[20] Right axis deviation is evidence of right ventricular hypertrophy. (See Figure 3) There could be features of ST changes showing some evidence of myocadiac infarction or biventricular hypertrophy.[21] Increase in central venous pressure and right atrial pressure with consequential right atrial hypertrophy may show features of P Pulmonale in the electrocardogram. Furthermore, Tall R wave in V_1 and deep S wave in V6 correlate with right ventricular hypertrophy. Microvolt T-wave alternans, Atrial or ventricular arrhythmias can also be seen in ECG if

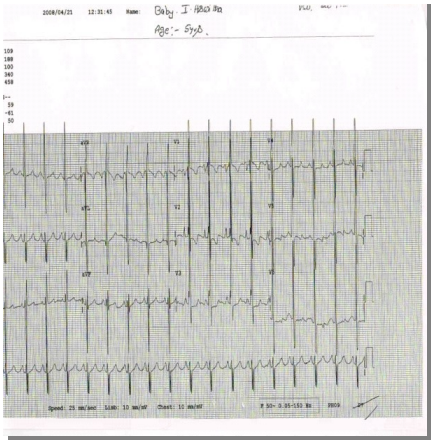

Fig. 3: Electrocardiogram of same Child showing Tachycardia, Normal Axis and Biventricular Hypertrophy.

there is an accompanying heart failure.[21] Valkovicova *et al*[22] have shown that combined ECG-Echocadiography analysis could be very vital in risk stratification in children with ES. They noted a compensatory RV hypertrophy as an important diagnostic tool in the management of children with ES. In their reportage, QRS duration > 120 ms was documented as a late marker in ES. They noted that a combination of QRS abnormalities with ECHO parameters could be used to determine patients who have a very high risk for clinical deterioration.[21] See Figure 3 showing ECG of a 5-year old child.

Echocardiography

This is a very important diagnostic tool in the evaluation of children with ES. [22–23]

Evidence of shunt reversal, dilated or hypertrophied right ventricle, alteration of right ventricular diastolic function, pericardial effusion, the

classical D sign on short-axis view, bowing of the interventricular septum to the left, paradoxical septal wall motion are features of pulmonary hypertension seen in children with ES.[22–23]

Pamela *et al*[23] documented some clinical and echocardiographic parameters in the diagnosis of ES. They assessed 181 subjects with ES, whose mean age was 39.1±12.8 years, follow-up of over 16.4 months, reported that tricuspid annular plane systolic excursion (TAPSE), myocardial performance, peak systolic velocity, and elevated central venous pressure as predictors of mortality in children with ES. The predictor outcome as documented by the authors includes, TAPSE <15 mm, Right atrial (RA) area ≥25 cm^2, a ratio of right ventricular effective systolic to diastolic duration ≥1.5, and ratio of RA to left atrial area ≥1.5.

A study had shown that type of defect can alter echocardiographic parameters in children with ES. For instance, in pre-tricuspid shunt, right atrial and right ventricular sizes were noted to be larger in children when compared with those with a post-tricuspid defects.[23] Furthermore, in children with ES, myocardial acceleration during isovolumic contraction was lower in subjects with pre-tricuspid shunts while the right ventricular function was better in children with post-tricuspid shunt. Among subjects with shunt defects, pulmonary acceleration time and right to left[24,25] was noted as the longest in subjects with patent ductus arteriosus (PDA).[23] See Figure 4.

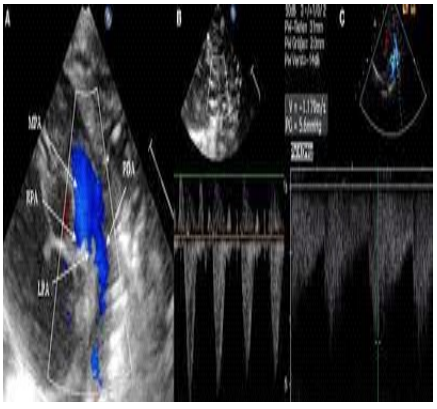

Fig. 4: Echocardiography of the same Child. Parasternal short Axis (Ductal) View showing a Large PDA Shunting Right to Left.

Computerized Tomography (CAT) Scan

The use of CAT scan in the evaluation of children with ES is useful in episodes of thrombo-embolic episodes. This could be evidenced when the child presents with epistaxis, haematochezia or cerebrovascular accidents. A Computerized axial tomography scan shows intra-luminal abnormalities in the pulmonary arteries and veins.[25–27] Wijesuriya *et al*[28] categorized the features of chronic pulmonary emboli in children with PAH into the vascular or parenchymal origin. Intra-luminal abnormalities such as totally or partially occlusive thrombi, webs, and bands have also been documented. Mosaic attenuation, pulmonary infarction, cavitation of infarcts, and broncho-pleural fistula have all been reported in thrombo-embolic episodes.

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) with contrast distinguishes pulmonary hypertension and pulmonary vascular disease from other diseases or other causes of mediastinitis.[29–32] In ES, MRI is important in delineating the dimension of right ventricular mass, volume, and function.[33–35] Shunt defects, sudden onset, and long standing pulmonary thrombo-embolic disease can be confirmed by the use of MRI.

Angiography

Children with ES usually present with pulmonary vascular disease and right heart catheterization and angiography are very important, especially in confirming operability. This permits the examination of the intra-cardiac structure and helps to exclude reversible causes of pulmonary hypertension. It also enables assessment of ventricular function, evaluation of the intra-cardiac shunt and determination of pulmonary vascular resistance. Hascoet *et al*[32] has noted haemodynamic prognostic predictive value in children with ES who have PAH. They noted in a study that diastolic pulmonary artery pressures of at least 45 mm Hg and World Health Organization (WHO) classification 3–4 of PAH denote disease progression and bad prognosis. The effects of vasodilators in the management of PAH in children with ES can be followed up with the use of Right heart angiography.[33–39]

In children with ES with pulmonary hypertension, angiography shows a large central pulmonary artery and attenuation of the peripheral vessels without any thrombi. Besides, cardiac catheterization can be of value in children with ES in confirming the severity of pulmonary arterial hypertension, conduit patency and pressure gradient, associated coronary artery anomalies (rare), and degree of shunting.[36–39]

Nuclear Imaging

This operates by the principle of particulate matter enhanced with technetium-99m. In primary pulmonary hypertension (PPH), the ventilation-perfusion ratio (V/Q) scan is usually normal. However, in children with ES with severe PAH and embolism, there is impaired perfusion.[40]

Histology

In patients with ES and severe pulmonary vascular disease, histologic analysis reveals abnormal extension of muscle into small peripheral arteries, severe medial smooth muscle hypertrophy of existing muscular arteries, plexiform lesions, and increased intercellular material, and a reduction in the overall concentration and size of arteries.

Staging

The pathologic changes of ES occur mainly in the pulmonary arterioles as highlighted by the Heath-Edwards classification. See Table 1.[9] Elevation in pulmonary arterial resistance to >12 Wood units suggests pulmonary vascular disease. This is resistance units indexed to body surface area. A ratio of pulmonary to systemic vascular resistance of > or equal to 1.0 defines ES.[41] Since the PVR is notably elevated at this stage, approaching the systemic level, the magnitude of the left-to-right shunt decreases. This results in the removal of the volume overload placed on the LV. Therefore, the size of the left ventricle and the overall size of the heart decreases, and the ECG evidence of left ventricular hypertrophy disappears, leaving right ventricular hypertrophy

because of the persistence of pulmonary hypertension.[41]

Table 1: Heath-Edwards classification[42]

Potentially Reversable

1 The medial thickness of the muscular pulmonary arteries and muscularization of the pulmonary arterioles without intimal alterations.
2 Together with the medial hypertrophy, intimal thickness with cell proliferation in the smaller muscular pulmonary arteries.
3 Intimal obstruction with concentric or eccentric masses of less cellular fibrous tissue in the arterioles and small muscular arteries. Large elastic arteries show atherosclerosis.

Usually Irreversible

4 Progressive dilatation of the small arteries with plexiform lesions and muscle hypertrophy is less apparent.
5 Chronic dilatation of the small arteries with plexiform and angiomatoid lesions.
6 Necrotizing arteritis with thrombosis.

Treatment

The management of children with ES is achieved by the use of vasodilators. Studies in randomized controlled trials have shown endothelin receptor antagonists such as bosentan, phosphodiesterase inhibitors, and prostanoids as drug treatment of choice in the treatment of children with ES.[42–44] European Association of cardiologists has recommended the initiation of these drugs in children whose histology is class 3.[45]

However, the use of functional classification in the treatment of children with ES may be clouded by the fact that it tends to underestimate the functional status and disease severity and conceals the importance of history and physical examination.[46,47]

Kalogeropoulos *et al*[48] has reported the use of B-type natriuretic peptide (BNP) concentration as a part of the periodic assessment of patients with PAH, and it has been recommended that echocardiographic and clinical scoring chart be used in children for treatment of PAH as this will help in robust prognostic assessment and optimization of advanced therapy.

The use of vasodilators in the treatment of children with ES has shown a marked improvement in exercise tolerance and 6-minute walk distance with improvement in pulmonary hypertension when compared with children with idiopathic PAH.[49]

Certain drugs have shown importance in the management of children with ES. For instance, long-term use of prostacyclin therapy has shown to improve cardiac index with a resultant decrease in PVR while Epoprostenol infusion had shown improved oxygenation and a 6-minute walk test.[50,51]

Similarly, Epoprostenol has shown to improve pulmonary pressure, oxygenation, and quality of life in children with ES while Bosentan, an endothelin-receptor antagonist has shown a marked improvement in oxygen saturation and NYHA classification in a cohort of 9 patients.[52–54]

Schulze-Neick *et al*[55] have shown that when, bosentan is taken orally twice daily, an associated improvement in 6 minutes walking distance and a decrease in systolic pulmonary artery pressure occur. Some studies have documented a delay in cardiac transplant in children with ES who were treated with prostacyclin analogs and/or endothelin receptor antagonists.[54]

In addition, sildenafil, a phosphodiesterase inhibitor has shown some safety in the treatment of ES. It has been documented to show improvement in walk exercise and a decrease in systolic pulmonary arterial pressure by 20mm Hg.[56]

A study by Vaidyanathan *et al*[57] and Mukhopadhyay *et al* (ref) have all documented improved oxygen saturation by sildenafil. The use of Nitric oxide replacement in the treatment of children with ES is not well elaborate.[58] Other therapies such as Imatinib, an anti-proliferative drug and Selexipag, a highly selective oral non-prostanoid IP2-receptor agonist, have been shown to markedly reduce complications of PAH in ES but its use in children is not well known.[59] Other symptomatic treatments of children with ES include the use of saline pharesis and ECMO for those with polycythemia or erythrocytosis, use of an anti-failure regimen for those in failure, drainage of abscess for those with brain abscess, and the use of infective endocarditis prophylaxis.[45]

The use of intravenous fluids should be done with caution and extreme case of dehydration should also be avoided as this may worsen the already existing cyanosis.[56–58]

Gerhard-Paul *et al*[59] has recommended the use of disease targeting therapies (DTT) in the treatment of ES with a good outcome. In this study, 153 patients with ES were treated with at least one DTT such as Bosentan or Sildenafil while a small percentage was placed on combined DTT. Other DTT used in some of their subjects were digoxin, angiotensin-converting enzyme-inhibitors, angiotensin receptor blockers, and β-blockers. Besides, plecebos (Oral anticoagulants and Aspirin) were given to a minor population of their subjects.

Oxygen Therapy

Though there is no clear evidence of improvement of cardiac function with oxygen supplementation. However, it is reported that Oxygen therapy causes an increase in pulmonary functional capacity, six-minute work exercise, and right ventricular function in children with ES.[54–58]

Anticoagulation

Anti-coagulation is not routinely used in children with ES and has been associated with iron deficiency.[56–58]

Surgery

Children with congenital heart defects should have corrective surgery as early as possible since no surgical closure of defects is possible once ES has developed.[56]

Atrial septostomy could be helpful for children with systemic or supra-systemic pulmonary artery hypertension and right ventricular diastolic failure. This could act as a pup-off valve and may help decongest the right ventricle.[56] The only surgical option available for children with ES is heart-lung transplantation, with or without repair of the shunt defects.[56]

Bilateral Lung Transplantation

Though the repair of the shunt lesion is needed, bilateral lung transplantation

is the treatment of choice for simple cardiac defects.[55–60] Bilateral lung transplantation does not cause transplant-associated coronary artery disease or graft rejection as against other types of transplants. Bilateral lung transplant is indicated in children with pulmonary hypertension and Eisenmenger syndrome who had surgically correctable congenital anomalies with good right ventricular function while heart-lung transplantation is reserved for children with ES with underlying single ventricle physiology or complex congenital anomaly and those with right ventricular diastolic dysfunction.[60]

However suicidal right ventricle (SRV) has been reported in children with ES who had lung transplants. Acute onset RVOT obstruction, otherwise known as suicide right ventricle (SRV) has been reported in some patients with ES who had undergone lung transplants.[53,54] Besides, SRV has been confirmed in an adolescent child with ES who had closure of a mid muscular and peri membranous VSD with a patent ductus arteriosus, who had bilateral lung transplantation.[60] An episode of severe RVOT obstruction with hemodynamic collapse was seen after the transplant. However, the child recovered after Extra Corporeal Membrane Oxygenation (ECMO) and relief of RVOT obstruction.[60]

Prognosis/Follow-up

Studies have shown that syncope, worsening right ventricular pressure, and systemic arterial desaturation below 85% indicate poor prognosis in children with ES.[50–60] Air travel should be taken with caution since reduced oxygen concentration and increased pressure could trigger deep venous thrombosis. This is worse in children and adolescents with thrombotic episodes.[60]

Pregnancy In ES

Females with ES of childbearing age die from complications of pregnancy. This could be due to pulmonary vascular reactivity and possible systemic hormonal changes.[50–60] The perinatal mortality rate in young women with ES is approximately 25%.[60] In fact, pregnancy is an absolute contra-indication in females with Eisenmenger syndrome.[60] The first week of delivery is documented as the most crucial period of reported maternal deaths.[60]

Contraception in ES

Oral contraceptive (OC) use is an absolute contraindication in patients with ES. [58-60] The risk of thromboembolism is high with OC, especially the oestrogen containing OC. Combined oral contraception is associated with venous thromboembolism, myocardial infarction, and cerebrovascular accidents. Surgical option of contraception is also deleterious in EC. Intra- uterine devise may be safe for these group of patients.[58–60] Other contraceptives that proved to be safety in subjects with ES include controlled-release levonorgestrel or norethindrone, implants, the use of diaphragms and cervical caps.[58–60]

Air Travel in ES

Children with ES cope with desaturation at an atmospheric pressure of 760 mmHg and atmospheric oxygen partial pressure of 159 mm Hg[58–60] Altitudes above 2,500–3,000 meters worsens vasoconstriction and severe hypoxia with worsening cyanosis and dyspnoe.[28,58–60]Broberg *et al*[59] however had reported cases of safety among frequent air travelers who had ES. Attenuation of low oxygen tension by a shift in the oxygen-haemoglobin dissociation curve could account for this.[58–60]

ES in a Developing Country

ES is very rare in developed country with only 3–4 cases seen per centre per year. This could be due to the advances in surgical treatment in developed country. It is documented that in developed country, about 8% of CHD patients had ES in the 1950s compared with only 1% of CHD seen currently. The prevalence of ES may be higher in developing country due to late presentation, late diagnosis and financial burden on the parents of these children in managing congenital heart disease.[58–60] In Nigeria, priority is placed in the treatment of tropical diseases such as malaria,Tuberculosis and HIV, thus neglecting children with congenital heart disease. This is because there is no strong policy regarding holistic management of children with congenital heart disease in the country.[58–60] The diagnostic workup in children with ES is painstaking as only a few laboratories exist in the country for catheterization coupled with the high cost of doing such procedures.[58–60] Even the cost of echocardiography at times is not within the reach of many parents of children with congenital heart diseases, since these diseases are common among low or poor socio-economic class.[58] Besides, heart lung transplant which is definitive is not common in developing country and the use of drugs becomes common place. The Quality of life in children with ES is very low compared with those seen in developed countries.[58–60]

CONCLUSION

Eisenmenger syndrome is a preventable disease that can be curbed early by diagnosis and treatment of congenital heart disease, especially in the developing world.

Declaration

Consent to Participate

Informed written consent for pictures of the 5-year-old child was also granted by the parents/caregivers before use.

Consent for Publication

Not applicable.

Competing Interest

We declare no competing interests.

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