Ivemark Syndrome

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Ivemark syndrome is a rare disorder of right heterotaxy which affects multiple organ systems of the body as a result of lateralization defects with situs inversus, asplenia or polysplenia due to defective left-right axis development, which is considered as the primary developmental field defect, characterized by cardiac and other organ abnormalities such as midline liver, right sided gastric fundus, inverted duodenal loop, with increased predisposition in males is reported in a female baby. This life threatening condition with severe complex cyanotic congenital heart disease compounded by the increased susceptibility to fatal infections due to immuno-compromise as a result of asplenia is the usual cause of death in early neonatal life. There is however no cure for Ivemark syndrome and management requires a multidisciplinary approach of surgical repair of cardiac malformations, protective immunization, antibiotic prophylaxis with aggressive treatment in event of any infections, may decrease the risk of morbidity and mortality.

Key Words: : *Ivemark syndrome, heterotaxy syndrome, cardiac anomalies, asplenia, infection, antibiotic prophylaxis, immunization*

Ivemark syndrome is a rare embryological disorder, with very few, about five to six cases described in literature [1,2], Martin first observed in 1826 heterotaxy syndrome consisting of splenic agenesis with congenital cardiac malformation and partial situs inversus [3], later Ivemark in 1955 reported 0.1 percent of asplenia syndrome out of 7,032 necropsies [4]. Incidence is approximately 1 in 10,000-40,000 births with autosomal recessive inheritance, though multiple factors both genetic and environmental play a role in the development of the Ivemark syndrome which may occur either sporadically or in many members of the same family and is usually diagnosed in neonates [5-7].

Congenital heart diseases usually affect about 0.75%-0.9% of newborns [8], which is the leading cause of death in neonates and infants, however heterotaxy syndromes (HS) are the most complex in about 1 to 5,000-7,000 of live births with cardiac defects, though 5%-10% of these patients do not have major cardiac malformations, making diagnosis difficult, usually confirmed at autopsy with asplenia being the revealing element for the diagnosis. Mortality is high, due to severe cyanotic cardiac defects compounded by asplenia resulting in fatal infection to encapsulated organisms such as Streptococcus pneumonia, Haemophilus influenza, and Meningococcus [9-11].

Prenatal diagnosis by fetal ultrasound detects specific organ abnormality, lack of a spleen and the presence of heart defects which is confirmed by fetal echocardiography. Postnatal diagnosis of Ivemark syndrome is made based on detailed patient history, a thorough clinical evaluation, identification of characteristic symptoms and a variety of specialized tests such as ultrasonography, computerized tomography, magnetic resonance imaging, scintigraphy for absent spleen and echocardiogram to detect heart defects [12]. The presence of Heinz or Howell-Jolly bodies, which are small fragments of DNA found in red blood cells on peripheral blood smear, indicates asplenia [13,14]. Though prenatal diagnosis of heterotaxy syndrome does not improve survival, it allows for appropriate counseling for families, facilitating prompt treatment.

CASE REPORT

A single live term baby girl was born by forceps delivery, to a second gravida mother, with no external congenital malformations. The first pregnancy had resulted in twin girls, both of whom died in the late neonatal period of diarrheal infections. The baby established spontaneous respiration at birth, but within two hours developed cyanosis with respiratory distress and hypothermia. A chest radiograph showed a midline cardiac shadow and gastric fundal shadow on the right. The baby's condition rapidly deteriorated, and she died at seven hours of age [15]. Autopsy revealed the viscero-atrial situs was ambiguous

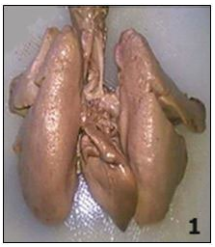

Figure 1) *Heart situated toward the midline.*

Figure 2) P*ulmonary dextro-isomerism with bilateral tri lobed lungs.*

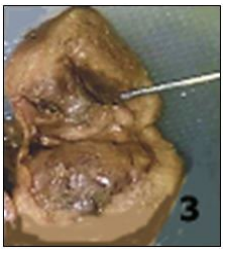

Figure 3) *The eparterial bronchi, branches superior to the first lobar division of the pulmonary artery*

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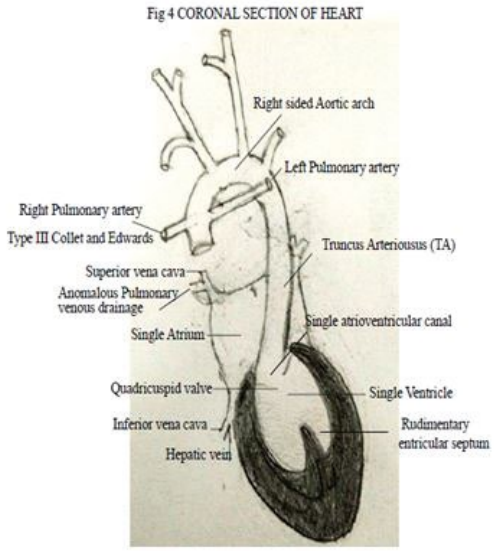

Figure 4) *Coronal section of heart.*

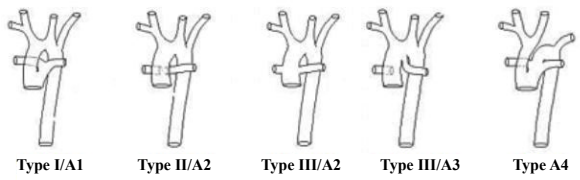

Figure 5) *Anatomic subtypes of truncus arteriosus.*

The atrium was single and received both the systemic venous via the superior and inferior vena cavae and the anomalous pulmonary venous return. The hepatic veins drained into the inferior vena cava. The ventricle was single with a shallow apical chamber and a rudimentary septal ridge with single atrioventricular communication guarded by a quadricuspid valve (Figures 1-3).

The aortic arch was right sided; the two lateral pulmonary arteries arose from the lateral aspect of the truncus, type III of Collet and Edwards [16] or Type A2 classification proposed by Van Praaghs in 1965 [17], namely the separate origin of the branch pulmonary arteries from the left and right lateral aspects of the common trunk. Schematic representation of coronal section of heart is shown in Figure 4.

DISCUSSION

Ivemark syndrome or right heterotaxy syndrome is due to a primary defect in lateralization resulting in situs ambiguous or right isomerism of internal organs [1,2,7]. Normally in situs solitus the heart, spleen, and pancreas is on the left side of the body and most of the liver is to the right while in situs inversus the orientation of the internal organs is completely flipped from right to left, often causing serious health problems. The two types of Heterotaxy syndromes is right isomerism with asplenia known as Ivemark syndrome which occurs more commonly in males, associated with severe cyanotic heart disease has poor outcome, while polysplenia or left isomerism more common in females with benign acyanotic heart defects has a better prognosis, although two bilobed lungs may indicate more severe lung issues [18,19]. Multiple different factors are believed to cause the development of laterality disorder, however Asplenia and polysplenia are now considered as part of the same wide spectrum as primary ciliary dyskinesia may be associated with either type [20].

The cardiac anomaly is due to the persistence of embryonic truncus arterious with failed septation forming a single ventricle with pulmonary arteries arising directly from the common trunk, in one of the several patterns, precluding a ductus arteriosus for fetal circulation. The most well-known classification was the fourfold system of anatomic classification of Truncus arteriosus (TA), developed by Collet and Edwards in 1949 [16] distinguishing the branching pattern of the pulmonary arteries. Van Praaghs in 1965 [17] described four primary types which includes the above Collet and Edwards's scheme [16] is another well-known commonly cited classification.

Controls Collet and Edwards's classification [16]

Type I	A single pulmonary trunk arising from the left lateral aspect of the common trunk and branching of the left and right pulmonary arteries.
Type II	Left and right pulmonary arterial branches have separate origins from the posterolateral aspect of the common arterial trunk.
Type III	Branch pulmonary arteries originate independently from the common arterial trunk or aortic arch, most often from the left and right lateral aspects of the trunk, occasionally one pulmonary artery arises from the underside of the aortic arch, usually from a ductus arteriosus as in this case.
Type IV	No pulmonary arterial branch arising from the common trunk is now recognized to be a form of pulmonary atresia with ventricular septal defect rather than truncus arteriosus. The "Type IV" proposed in 1949 is no longer considered a form of persistent truncus arteriosus (PTA).

Van Praaghs classification [17]

Type A1	Is identical to the type I of Collet and Edwards.
Type A2	Includes Collet and Edwards type II and most cases of type III, namely those with separate origin of the branch pulmonary arteries from the left and right lateral aspects of the common trunk.
Type A3	Includes cases with origin of one branch pulmonary artery usually the right from the common trunk, with pulmonary blood supply to the other lung provided either by a pulmonary artery arising from the aortic arch (a subtype of Collet and Edwards type III) or by systemic to pulmonary arterial collaterals.
Type A4	Is defined not by the pattern of origin of branch pulmonary arteries, but rather by the coexistence of an interrupted aortic arch. In the vast majority of cases of type A4, which fall into the type I of Collet and Edwards, the pulmonary arteries arise as a single pulmonary trunk that then branches. In any of these patterns, intrinsic stenosis, hypoplasia, or both may be present in one or both branch pulmonary arteries, which may have an effect on management and outcome.

The Anatomic subtypes of truncus arteriosus (TA), according to the classification systems of both Collet and Edwards (I,II,III) and Van Praaghs (A1,A2,A3,A4) combined is shown in the image below (Figure 5) [16,17].

Clinical symptoms of Ivemark syndrome depends upon the specific cardiac defects such as cyanosis, heart murmurs, and signs of congestive heart failure which is life-threatening with high mortality during infancy. The major cardiac defects in Ivemark syndrome or right isomerism typically include a single ventricle or large ventricular septal defect, a single atrium, and an atrioventricular connection often associated with atrioventricular valve regurgitation, truncus arteriousus with common AV valve, multiple sinus nodes, endocardial cushion defect. Both systemic and pulmonary venous drainage which may be either total or partial anomalous (TAPVR/PAPVR), with pulmonary stenosis or atresia, characteristically, the inferior vena cava (IVC) and the abdominal aorta have a common course, with the abdominal aorta being juxtaposed to the IVC, together traverse the midline just below the diaphragm to enter a common atrium. Bilateral superior venae cavae (SVC) drain into a common atrium with features of bilateral right atria [18,19,21-23].

Minor cardiac defects in around 5-10% of the patients include dextrocardia, atrioventricular septal defect (AVSD), Secundum atrial septal defect (ASD), Coartation or aorta, single atrioventricular valve regurgitation grade 1-2, left atrioventricular valve (LAVV) regurgitation; ventricular septal defect (VSD) is associated with longer survival. Sudden death due to cardiac arrhythmias may potentially be related to major causes of late mortality [21-23] while death in the first year of life is caused by cardiac failure compounded by fulminant sepsis due to asplenia [9,10,21-24].

The abdominal defects associated with Heterotaxy include: symmetrical/ transverse midline liver, duodenal atresia, multiple or absent spleen, or spleen abnormality, midline gallbladder, agenesis of the gall bladder, biliary atresia which may cause jaundice, pancreatic malformation, annular pancreas, or

pancreatic aplasia with total pancreatic insufficiency including insulin apart from digestive enzymes would be an additional complication. Complete common mesentery rotation, with colon situated entirely on the left side, the small intestine and stomach on the right side, symptoms of sudden, severe pain in the abdomen is often due to abnormal twisting or volvulus of the intestines, a small stomach and imperforate anus. Genitourinary anomalies include horseshoe kidney, fused/absent left adrenal gland, bicornuate uterus and bilobed urinary bladder. Other health issues associated with Heterotaxy include scoliosis, eye sight problems, and clubbing, deficiency of serum IgM and IgE, reversal of the frontal and occipital petalia, crossed diastasis, agenesis/malformation of the corpus callosum, left cerebral hemisphere language dominance and strong right-handedness [19,21-24].

The roentgenographic features of Ivemark syndrome include a markedly symmetrical liver [25], a midline stomach bubble, malrotation of the bowel, lack of spleen, bilateral eparterial bronchi, bilateral trilobed lungs and symmetry of the tracheobronchial tree with decreased pulmonary vascularity or pulmonary atresia, mesocardia, is common, but sometimes dextro or laevocardia and bilateral right atria. Vascular anomalies include superior vena caval duplication, absent coronary sinus, and juxtaposition of the inferior vena cava usually in front of the abdominal aorta. The abdominal aorta and inferior vena cava usually lie on the same side [26-30]. Two sinoatrial nodes may be present; the electrocardiogram may show either an inferior right-ward, or inferior left-ward P axis. The same patient may show each at different times. Although all cases of asplenia have an atrioventricular canal, the QRS axis in cases exhibiting a single ventricle may be inferior and right-ward, while cases with two ventricles usually have a superior QRS axis [21-24].

Etiology

The causes of Ivemark syndrome may be due to multiple factors such as sporadic, hereditary, and environmental. Sporadic cases have isolated individual affected in a family with unknown cause as no identified gene mutations or other risk factors identified [5-7]. Thus hereditary or genetic inheritance is autosomal dominant or recessive, indicating a male preponderance of this syndrome, or may be X-linked. In autosomal dominant inheritance one copy of the altered gene in each cell is sufficient to cause the disorder, while autosomal recessive requires two copies of the mutated gene, one from each carrier parent who typically do not show signs and symptoms of the condition occurs as a feature of primary ciliary dyskinesia [20].

In X-linked inheritance, the mutated gene located on X chromosomes, one of the two sex chromosomes in each cell is attributed to the zinc finger protein of cerebellum 3 (ZIC3) gene [31,32]. In addition failure to establish normal left-right asymmetry with right heterotaxy, congenital heart disease and asplenia or non-functional polysplenia, is attributed to mutations of the connexin 43 gap junction genes [33]. However careful genetic study supports a multifactorial inheritance. Environmental factors affecting a woman during pregnancy may also contribute to the risk of heterotaxy syndrome in the child such as diabetes mellitus, smoking and exposure to hair dyes, cocaine, and certain laboratory chemicals [34,35]. Though isolated congenital asplenia is a very rare, the mode of inheritance is autosomal dominant with ribosomal protein SA haploinsufficiency, however a few sporadic cases have been reported [36].

Though the exact timing embryologically is not known, most of the abnormalities in the asplenia syndrome can be linked to horizon XIII, a developmental stage of the embryo that corresponds to approximately 28 days gestation and 28 somites, when the primitive heart and venous connections form. Disruption of this early embryologic event, when the cardiac chambers are incompletely septated, indicates the preponderance of common atria, single ventricles, abnormal pulmonary venous connections, and conotruncal anomalies observed in heterotaxy syndrome [5-7,34-36].

Mutations of certain genes are essential for the development of left-right asymmetry involved in heterotaxy disorders, as the proteins produced from these genes play a role in determining which structures should be on the right side of the body and which should be on the left, during the earliest stages of embryonic development, rarely, chromosomal changes such as insertions, deletions, duplications, and other rearrangements of genetic material have been associated with this condition [37].

Important genes implicated [5-7,31-35,37-40] include:- Heterotaxia NODAL location 10q22.1 sequence chromosome 10; NC_000010.11 (70431936.70447948, complement), Total number of exons 5, or nodal growth differentiation factor gene which encodes secreted ligand of the TGF-beta (transforming growth factor-beta) superfamily of proteins that regulates early embryonic stem cell pluripotency, left-right heterotaxy and also may play a role in human placental development.

Heterotaxia CFC1 location 2q21.1 sequence chromosome 2; NC_000002.12 (130592165..130599575, complement) Total number of exons 7 or cripto, FRL-1, cryptic family also known as HTX2; CFC1B; DTGA2; CRYPTIC gene is involved in signaling left-right embryonic axis, mutations causes defects in organ development, including autosomal visceral heterotaxy and congenital heart disease. Encoding also a member of the epidermal growth factor (EGF)-Cripto, Frl-1, and Cryptic (CFC) family, involved in signaling during embryonic development, mutations causing defects in organ development, including autosomal visceral heterotaxy and congenital heart disease.

Heterotaxia FOXH1 location 8q24.3 sequence chromosome 8; NC_000008.11 (144473732.144476335, complement), Total number of exons 3, gene encodes the human homolog of Xenopus forkhead activin signal transducer-1. FOXH1 protein binds SMAD2 and activates an activin response element via binding the DNA motif TGT(G/T)(T/G)ATT.

Heterotaxia ZIC3 location Xq26.3 sequence chromosome X; NC_000023.11 (137566127.137577691), total number of exons 4, or Zic family member 3 (Xq26.3), Gene ID: 7547, also known as HTX; HTX1; ZNF203; VACTERLX which encodes a member of the ZIC family of C2H2-type zinc finger proteins is a nuclear protein that probably functions as a transcription factor in early stages of left-right body axis formation. Mutations in this gene cause X-linked visceral heterotaxy, which includes congenital heart disease and left-right axis defects in organs.

Also ACVR2B gene or activin A receptor type 2B, regulates many physiological and pathological processes, CFAP53 gene or cilia and flagella associated protein 53 mutation causes visceral heterotaxy-6, influences the beating of primary cilia hence involved in the establishment of organ laterality during embryogenesis. CITED2 gene or Cbp/p300 interacting transactivator with Glu/Asp rich carboxy-terminal domain 2 protein encoded by this gene inhibits transactivation of HIF1A-induced genes by competing with binding of hypoxia-inducible factor 1-alpha to p300-CH1. Mutations in this gene cause cardiac septal defects and may play a role in mesoderm and/or neural patterning during gastrulation. CRELD1 gene or cysteine rich with EGF like domains 1 gene mutations causes atrioventricular septal defect.

DNAH5 gene or dynein axonemal heavy chain 5 produces dynein protein that functions within the cilia of cells, allowing coordinated back and forth movement to move the cell or the fluid surrounding the cell. DNAH11 gene or dynein axonemal heavy chain 11 gene encodes a ciliary outer dynein arm protein involved in the coordinated movement of respiratory cilia. Dynein has ATPase activity; the force-producing power stroke is thought to occur on release of ADP. Mutations cause Kartagener Syndrome.

GATA4 gene or GATA binding protein 4 gene encodes a member of the GATA family of zinc-finger transcription factors which regulates genes involved in embryogenesis and in myocardial differentiation and function, is also necessary for normal testicular development. Mutations in this gene have been associated with cardiac septal defects. GDF1 gene or growth differentiation factor 1 gene may be responsible in the establishment of left-right asymmetry in early embryogenesis and in neural development in later embryogenesis.

GJA1 gene or gap junction protein alpha 1 gene provides instructions for making a protein called connexin 43, which is one of 21 connexin proteins that play a role in cell-to-cell communication by forming channels, or gap junctions, between cells. Gap junctions allow for the transport of nutrients, charged particles (ions), and other small molecules that carry necessary communication signals between cells.

LEFTY2 gene or left-right determination factor 2 gene encodes a secreted ligand of the TGF-beta (transforming growth factor-beta) superfamily of proteins which plays a role in left-right asymmetry determination of organ systems during development. Mutations in this gene have been associated with left-right axis malformations, particularly in the heart and lungs. NAT10 gene or N-acetyltransferase 10, the protein encoded by this gene is an RNA cytidine acetyltransferase involved in histone acetylation, tRNA acetylation, the biosynthesis of 18S rRNA, and the enhancement of nuclear architecture and chromatin organization. Acetylates alpha-tubulin, may affect microtubule stability and cell division.

NKX2-5 gene or NK2 homeobox 5 gene encodes a homeobox-containing transcription factor functions in heart formation and development. Mutations in this gene cause atrial septal defect with atrioventricular conduction defect, and also tetralogy of Fallot. In addition is required for

spleen development and also causes congenital hypothyroidism, non-goitrous type 5, a non-autoimmune condition. SESN1 gene or sestrin 1 gene encodes a member of the sestrin family that may play a role in the cellular response to DNA damage and oxidative stress.

SHROOM3 gene or shroom family member 3 gene encodes protein that may be involved in regulating cell shape in certain tissues. SMAD2 gene or SMAD family member 2 gene encodes SMAD proteins which are signal transducers and transcriptional modulators that mediate multiple signaling pathways regulating multiple cellular processes, such as cell proliferation, apoptosis etc.

Differential diagnosis includes:

a) Kartagener syndrome with complete reversal of the internal organs, situs inversus with dextrocardia and underdevelopment or lack of a spleen (asplenia) is inherited as an autosomal recessive trait, with defects in movements of the cilia, or thin hair-like structures covering most of the cells in the respiratory tract which fail to clear the respiratory passages of mucus and other secretions causing rhinitis, sinusitis, chronic otitis media, and bronchiectasis [1,20].

b) X-linked visceral heterotaxy is a rare genetic disorder characterized by various heart defects, dextrocardia, complete reversal of the internal organs or situs inversus viscerum and asplenia or polysplenia, caused by disruptions or mutations to the zinc finger protein of cerebellum 3 (ZIC3) gene located on the X chromosome [31,32,38].

Mortality is high and most patients with Ivemark syndrome die before one year [9-11,41], due to severe complex congenital heart disease, right atrial isomerism or functional single ventricle undergoing single ventricle reconstruction continue to have a high mortality despite modern surgical techniques, further compounded by severe infections due to immuno-compromise of absent spleen [42,43]. Hence the importance of careful examination of peripheral blood smears in children with congenital heart disease to indicate splenic function by assessment of RBC pitting i.e. the presence of Heinz or Howell-Jolly bodies in peripheral blood smear, in addition, the size and number of platelets should also be noted, thrombocytosis may be present in individuals without a functioning spleen, while those with certain immunodeficiency, such as Wiskott-Aldrich syndrome may present with thrombocytopenia and abnormally small platelets [12-14]. Accurate diagnosis of asplenia/polysplenia is confirmed by radio-isotype scanning and direct functional-anatomic assessment by radionuclide splenic scanning with use of ^{99m}Tc sulfur colloid or tagged heat-damaged RBCs [12].

Spleen is a part of the body's lymphatic system to help fight against severe bacterial infections that has a number of immunologic functions including phagocytic function clearing microorganisms such as encapsulated bacteria, protozoa, senescent cells, and immune complexes from the blood and the presence of marginal zone B cells that produce specific protective antibody. The increased susceptibility to infection such as meningitis or fulminant septicemia is a constant hazard of asplenia, with inability to opsonize polysaccharide encapsulated bacteria such as Streptococcus pneumonia, Haemophilus influenza, and Meningococcus from circulating blood, often fatal within a few hours, further compounded by deficiency of T-cell independent antibodies to polysaccharide capsule of Streptococcus pneumonia [9-11,44-49].

A study comparing thirteen patients with asplenia to twelve age-matched patients with congenital heart disease but without evident splenic problems, revealed that IgG, IgA, IgM and C3 and C4 values were normal for age in all subjects studied, but the T cell subsets, including the percentage of CD3 and CD4 cells and the CD4/CD8 ratio were significantly less in patients with asplenia compared to controls (P<0.01, respectively). The lymphoproliferative responses to mitogens (ConA, concanavalin A, phytohemagglutinin and pokeweed mitogen) were also decreased in asplenic patients. Fc-mediated clearance of sensitized autologous erythrocytes was significantly impaired in patients (n=13) when compared with age-matched controls (n=5) (clearance $t_{1/2}$ 59.0+/-9.6 minutes vs. 12.5+/-1.6 minutes, P<0.001). Thus profoundly impaired reticuloendothelial clearance and decreased T cell function might account for the life-threatening infections frequently seen in patients with congenital asplenia syndrome; IgE was also decreased in one patient [44-49].

Hence vaccine induced immunity may be also be defective in asplenic patients due to lack of adequate T-cell-dependent responses which is associated with long-lasting immunologic memory against polysaccharide vaccines. However in all age groups, the lack of adequate specific protective antibody associated with opsonophagocytic deficiency is the major risk factor, but incidence of invasive pneumococcal infection peaks in young children aged less than two years due to immature immune system, with a second equal peak in adults aged above 65 years. Similarly meningococcal infection causes meningitis and sepsis including other morbidities such as limb amputations, strokes, and neurocognitive abnormalities which may occur at all ages, but also has a peak incidence in children aged below two years, due to lack of protective antibody or, rarely, IgA antibodies that block serum anti-neisserial bactericidal activity [9-11,44-52].

However asplenia is not a contraindication to administration of any vaccine, despite suboptimal responses to immunization, despite polysaccharide vaccines against S. pneumoniae (23-valent), designed to stimulate long-lasting immunologic memory, infections by serotypes out of the content of heptavalent pneumococcal vaccine may occur and three fourths of the serotypes present in the current 23 valent polysaccharide vaccine are resistant to antibiotic therapy, therefore vaccination is still recommended in asplenic individuals in spite of inadequate T-cell-dependent responses, still has some immunologic memory to serotypes that cause 80% of invasive pneumococcal disease in children including serotypes that are most resistant to antibiotic therapy. Other vaccines include N. meningitidis (quadrivalent), and conjugate vaccines against H. influenzae with revaccination every five years for S. pneumoniae and every three years for N. menigitidis, though revaccinations against H. influenzae is generally not recommended [50,51].

Though asplenic patients have poor vaccine or immunological response or failure, with antibody values declining more rapidly than in those still possessing a spleen, will benefit from booster immunizations especially in relation to the pneumococcal polysaccharide vaccine which in contrast to the accepted protective antibody value for H. influenzae type b, has no agreed protective titre against S. pneumonia. Also the current measurement of pneumococcal antibodies which gives total against the 23 valent polysaccharide vaccine may indicate a good response against one serotype and mask a failed or poor response to other serotypes. However the decision for timing of booster immunizations though difficult may be based on antibody titre measurement. The optimal frequency for checking antibody measurement is pre-immunization, one month later and then at three and five years post-immunization, or alternatively three week post-immunization and then at yearly intervals. Thus individuals who fail to respond could be targeted for other measures such as maintaining lifelong antibiotic prophylaxis [44,45,48,50,51].

The recommendation of antibiotic prophylaxis as well as immunization for pneumococcal infections and Haemophilus influenzae type b will increase protection from invasive infections. However all fever of unknown origin must be evaluated carefully in asplenic patients and treated [52-55]. In a study four of five cases of asplenia with antibiotic prophylaxis and immunization for encapsulated bacteria, did not require hospitalization for infection diseases during the follow-up period of 5-40 months, though one died later of complex cardiac malformations [11].

Vaccines in children

Primary immunization in immunocompromised children is important as they are at increased risk from vaccine preventable diseases (VPD). Routine immunization and vaccines critical in cases of asplenia, include influenza vaccine annually to protect against seasonal flu, which also helps prevent secondary bacterial infection 54. Tdap vaccine to protect against whooping cough and tetanus, Hib vaccine to protect against Haemophilus influenzae type b (Hib), Pneumococcal vaccines to protect against pneumonia and other pneumococcal disease. Meningococcal vaccines protects against meningitis and other meningococcal disease, MMR vaccine which protects against measles, mumps, and rubella. Varicella vaccine protects against chickenpox prevents congenital malformations. Zoster vaccine protects against shingles if sixty years or older, HPV vaccine protects against human papillomavirus is administered in adolescent girls and also in men up to twenty one years and women up to twenty six years [53,54].

Vaccines in pregnant women

Pregnancy is associated with unique and heightened susceptibilities to greater morbidity and mortality from a variety of bacterial and viral vaccine-preventable diseases with adverse pregnancy outcomes such as spontaneous abortion, congenital anomalies, preterm birth, fetal growth restriction, low birth weight, fetal distress and demise. Thus vaccination to pregnant women, not only prevents maternal infection, but also offers fetal and infant benefit through passive immunization by transplacental transfer of maternal IgG antibodies as well as IgA antibodies in breast milk improving maternal-child health [56].

It is the potential for passive immunization in protecting young infants

against pertussis infection that has been the primary driver for the recent recommendation for administration of tetanus, diphtheria, acellular pertussis (Tdap) in each and every pregnancy, regardless of earlier Tdap, as passive immunization of vaccine-induced antibodies across the placenta into the fetal circulation can protect young infants during the first few months of life when they are most vulnerable to pertussis and prior to establishing immunity from their own primary vaccination series [57,58].

Pneumococcal polysaccharide 23-serotype vaccine (PPSV23) provides protective antibody levels for at least one year following delivery with higher neonatal antibody levels, although serum anti-polyribosylribitol phosphate (PRP) and anti-6B-type pneumococcal antibodies are below the levels for protective activity when compared to after natural infections, in fact two (6B and 19F) of seven serotype-specific pneumococcal antibodies were not elevated to protective levels after the second 7-valent pneumococcal conjugate vaccine (PCV7) therefore, third PCV7 was added, though anti-PRP antibody was significantly increased after Hib vaccination. Nevertheless, CDC guidelines recommend PPSV23 immunization, should be given to pregnant women. Also meningococcal tetravalent polysaccharide vaccine (MPSV4), in the third trimester gives longer duration of vaccine-induced immunity compared to MCV4 [44,45,50,51].

Perinatal transmission of Hepatitis B virus (HBV) which causes chronic disease necessitates routine screening for surface antigen (HBsAg) in pregnant women and neonatal treatment with HB immunoglobulin (HBIg) prophylaxis with HBV vaccination during the first hours of life for infants born to HBV infected mothers. Three-doses of HBV vaccine should be given for previously unvaccinated or incompletely vaccinated pregnant women with risk factors for HBV infection. Recombinant hepatitis B vaccine as well as inactivated hepatitis A vaccine that protects against Hepatitis A virus (HAV) infection are safe during pregnancy as it does not contain live virus components and unlikely to carry any risk of maternal or fetal harm [59].

Maternal influenza immunization with inactivated influenza vaccine (IIV) has great potential to improve maternal health during pregnancy and the immediate postpartum period when the risks of influenza are greatest as a result of pregnancy-associated changes with immunological alterations in cell-mediated immunity and cardiorespiratory physiologic changes, causing higher rates of hospitalization, acute respiratory distress syndrome (ARDS), cardiorespiratory failure or death and adverse fetal outcomes [60,61]. Respiratory syncytial virus (RSV) is the leading source of bronchiolitis and pneumonia, causing hospitalization and recurrent wheezing or asthma in the first year of life, hence recombinant RSV vaccine would result in combined maternal and infant benefit due to higher RSV cord blood antibody titers [62].

Neonatal meningitis due to both Escherichia coli and group B streptococcal infections is associated with lack of specific maternal antibodies to either the K-1 capsule or capsular polysaccharide of streptococci, respectively correlated with deficiency of maternal or transplacental specific antibody resulting commonly in sepsis and meningitis in the event of invasive infection within the first three months of life. Group B streptococcal infections may cause asymptomatic cervico-vaginal colonization often leading to ascending intra-amniotic infection (IAI), with serious consequences of maternal pelvic infections, sepsis, postpartum hemorrhage and postpartum endometritis, while urinary tract infections may lead to acute pyelonephritis with adverse pregnancy outcomes of preterm birth, low birthweight, and fetal demise. Hence vaccine against GBS causes passive immunity, novel vaccines include trivalent group B streptococcus polysaccharide vaccine which aims at reducing infant infection through maternal immunization [63].

Thus immunization has become accepted as an integral part of the preventive strategy against serious infection in the asplenic population [53-56]. Though certain vaccines provide some protection, an adequate vaccine response cannot be assumed; therefore protection of the immunocompromised patient may require the use of passive immunization i.e. intravenous immunoglobulin as well as adjunctive measures, such as antiviral drug prophylaxis during influenza A outbreaks, prophylactic antibiotic therapy to reduce the incidence of infection or when infection does occur, aggressively treated with prophylaxis before certain surgical and dental procedures [55].

Travel measures

Scheduled immunization, especially Group A meningococcus is required for those visiting countries such as sub-Saharan Africa [64]. Malaria is a parasitic infection and babesiosis, a rare tickborne protozoal infection has similar clinical manifestations to malaria. Malaria is serious in asplenic patients as they have a delayed clearance of parasites from the bloodstream despite appropriate treatment [65]. Hence appropriate anti-malarial prophylaxis medication is needed with extra vigilance to prevent mosquito bites by using nets, repellent cream, etc. Chemoprophylaxis includes chloroquine for areas known to be fully chloroquine sensitive areas; others include mefloquine, chloroquine-proguanil, doxycycline, and atovaquione-proguanil. Prophylaxis should be started at least 1-2 weeks before departure and continued for four weeks after return except for atovaquone-proguanil which can be started on the day of departure. However those with fever, fatigue, and haemolytic anaemia require diagnostic confirmation by identification of parasites within red blood cells on blood film and by specific serology. Quinine (with or without clindamycin) is usually an effective treatment [64-66]. Animal bites, susceptible to capnocytophaga canimorsus infection which includes minor dog bites or other animal bites require adequate antibiotic cover and best treated with five-day course of amoxycillin/clavulanate 500 mg/125 mg PO bid, or erythromycin in patients allergic to penicillin [67].

In travel to intermediate and high-risk areas, individuals are treated for invasive bacterial prophylaxis with amoxycillin 250 mg-500 mg PO bid for duration of travel and "stand-by" treatment of febrile illness with amoxicillin 3 g PO stat, then 1 g PO thrice daily in the event medical attention is delayed. Prompt medical advice for management of fevers is essential; alternatives drugs include ceftriaxone 1 g IM/IV stat, then daily for five days or a quinolone PO (gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin). Asplenic individuals with babesiosis require treatment with a combination of clindamycin and quinine as chloroquine is ineffective. Pneumococcal vaccinations may not cover some of the other strains of pneumococcal bacteria present in other countries whose antibiotic resistance varies, hence requires a different choice of stand-by antibiotic [64].

A card with an alert warning stating asplenic status carried in the wallet or special bracelet or necklet worn, is essential, as it is not only as a constant reminder to the individual of the underlying condition, but also information of the asplenic state will be vital in the event of any medical emergency, as it would alert medical attendants and healthcare professional to take immediate action if they become ill.

CONCLUSION

Ivemark syndrome is a very rare embryological disorder of laterality with right heterotaxy, asplenia and severe complex cyanotic heart disease with a male predilection is reported in a female baby. High neonatal mortality is due to complex cyanotic cardiac defects and asplenia causing immune-compromise with increased susceptibility to fatal infections. However survival into adulthood can be explained by less severe cardiac defects, absence of arrhythmias or overwhelming infections. Hence there is no cure for Ivemark syndrome and management is directed toward specific symptoms, surgery to correct the various cardiac defects, proper protective immunizations, prophylactic antibiotic therapy to reduce the incidence of infection and when infection does occur, prompt medical advice for management with aggressive treatment will result in improved survival rates. Thus a multidisciplinary approach with coordinated efforts of a team of specialists such as pediatricians, surgeons, pediatric cardiologists, pediatric gastroenterologists, pulmonologists, neurologists, immunologists and other healthcare professionals may be involved to systematically and comprehensively plan an affected child's treatment.

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