CASE REPORT

ELLIS-van CREVELD SYNDROME IN A NIGERIAN WOMAN: A CASE STUDY

[1]AHMADU MS, [2]TALLEMA, [1]AHIDJO A, [1]TAHIR AA

ABSTRACT

Ellis-van Creveld (EVC) syndrome or chondroectodermal dysplasia is a rare, autosomal recessive disorder that was first described by Ellis and van Creveld in the mid-20th century.The syndrome is characterized by a tetrad of chondrodystrophy, post axial polydactyly, and hidrotic ectodermal dysplasia, mostly involving teeth and nails and a high frequency of congenital cardiac anomalies, most frequently a common atrium.There has been no documented case report of EVC syndrome from Nigeria in the literature. We, therefore, present a 30 year-old Nigerian woman who presented to our hospital with features consistent with this rare syndrome.

KEYWORDS: Ellis-van Creveld syndrome, Holt-Oram syndrome, Goldenhar's syndrome, Nigerian woman, atrial septal defect, polydactyly, carpal fusion, chest X-ray

INTRODUCTION

Ellis van Creveld(EVC) syndrome is a rare autosomal recessive disorder with variable phenotypic presentation[1]. In its classic presentation, it comprises of a tetrad of chondropathy, bilateral postaxial polydactyly, ectodermal dysplasia and congenital cardiac malformations[2]. The syndrome results from a mutation involving the EVC1 and EVC2 gene, both located on chromosome 4p16.The exact prevalence of EVC syndrome is not known. Though largely reported in the old order Amish community of Pennsylvania in approximately five in 1000 live births, the syndrome is now known to affect all races with an estimated birth prevalence of 7/1,000,000 in the general population[1,2]. Given the variable phenotypic patterns, the full spectrum of the disorder may be lacking in a given patient. However, the classic presentation includes disproportionate small stature with shortening of the middle and distal phalanges, bilateral (rarely unilateral) postaxial polydactyly of the hands (and occasionally the feet), malformation of the carpal bones, congenital heart defect (atrioventricular canal with common atrium) and hidrotic ectodermal dysplasia affecting the nails, hair and teeth[3]. There has been no report of a case of EVC syndrome from Nigeria in the literature.We, therefore, present a case of EVC syndrome in a 30 year-old Nigerian woman with short stature, bilateral postaxial polydactyly, fusion of the carpal bones, missing phalanges, hypoplastic nails, atrioventricular canal defects and single atrium.

[1]Department of Radiology, University of Maiduguri Teaching Hospital, Maiduguri, Nigeria
[2]Department of Internal Medicine, University of Maiduguri Teaching Hospital, Maiduguri, Nigeria

Correspondence to:
DR. AHMADU MUHAMMAD SANI
Department of Radiology, University of Maiduguri Teaching Hospital, PMB 1414, Maiduguri, Borno State, Nigeria
Phone:- +234 7055882425
eMail:- drahmadums@unimaid.edu.ng

CASE REPORT

A 30 year-old female was referred to the cardiac unit of the UMTH with two months history of progressive shortness of breath, palpitation, chest discomfort and leg swelling. She developed cough productive of whitish sputum a week prior to presentation. There

was history of orthopnoea and paroxysmal nocturnal dyspnoea. No history of fever, gastrointestinal or genitourinary symptoms. She has had paroxysms of palpitation with shortness of breath since childhood, necessitating hospitalization 15 years ago. She is a product of twin gestation, and the shortest in the family. The first child of her parents, a male, suffered hypoxia at birth and had extra digits in upper and lower limbs, and was lost to early neonatal death. Two other male siblings (also a product of twin gestation) have extra digits, but attained normal growth with no cardiopulmonary symptoms. She is single and works as a community health worker. She doesn't smoke cigarette nor drink alcohol.

When examined, she was breathless and centrally cyanosed, but not febrile. She had bilateral pitting pedal edema extending to mid shin, with grade II finger clubbing. She has six and seven digits on the left and the right hands respectively (Figure 1), with hypoplastic nails. Both hands, feet and the right second toe appear broadened, with two nails on the fifth left toe. The right second toe appears broadened. Facial appearance and hair distribution appeared normal. The teeth are widely spaced, but otherwise normal. The resting pulse was regular at 116 beats per minute with a normal volume. All other peripheral pulses were present and normal. Sitting blood pressure was 120/80mmHg. There was jugular venous distension with the uppermost column beyond the angle of the mandible in sitting position. The chest wall was asymmetric with a precordial bulge and increased activity. Point of maximal impulse was in the fifth left intercostals space lateral to mid clavicular line. There was a left parasternal heave, a left parasternal holosystolic murmur, a fixedly splitS_2 and a loud P_2. The respiratory rate was 36cycles perminute, with a central trachea and vesicular breath sounds. The abdomen was full, with right hypochondrial tenderness and ascites. No evidence of hepatomegaly was, however, noted.

A 12 lead resting ECG showed a heart rate of 117 beats per minute with a QRS axis of -90^o. There was a first degree AV-block and R/S >1 in V_1 suggesting RVH. There was a poor R-wave progression and negative/prolonged P wave in V_1 (left atrial abnormality). Transthoracic echo revealed situs solitus with appropriate ventriculoarterialconcordance and a single atrium. Right ventricle is thickened and dilated with interventricular septal flattening in systole and diastole, consistent with right ventricular pressure and volume overload.Right ventricular ejection fraction was >50% by TAPSE. The pulmonary arterial systolic pressure was 93mmHg. There was a moderate MR due to cleft in the anterior mitral valve leaflet. Aortic valve was normal. Coronary sinus was observed to be mildly dilated. However, venous connections were normal. Trans-oesophageal echo and cardiac MRI were not available in our centre. Complete blood count, ESR, BUN as well as routine electrolytes were normal.

Postero-anterior chest radiograph (Figure 2) showed cardiomegaly of right ventricular configuration (cardio-thoracic ratio = 60%) with rounding of the cardiac apex. There was prominence of the right pulmonary trunk. The ribcage was normal.

Plain radiograph of the hands (Figure 3) revealed six digits with a post-axial attachment of a hypoplasticseventh digit to the sixth digit on the right. There were no middle phalanges in the 3rd and 4th digits of the right hand. The left hand showed six well developed digits. Fusion of the hamate with capitate was noted in both hands. Plain radiograph of the feet (Figure 4)showed six digits in the right foot with fusion of the 2nd and 3rd proximal phalanges at their bases. The left foot showed five rows of metatarsals with the 4th metatarsal having two proximal phalanges. The tarsal bones were normal. Ultrasound scans of the abdomen and pelvis were normal.

Based on the clinical findings, radiographic abnormalities in the chest, hands and feet, echocardiographically proven atrial septal defect, family history of polydactyly and neonatal death from a possible congenital heart disease, a diagnosis of a variant of Ellis-van Creveld (EVC) syndrome presenting with Eisenmenger syndrome was made. She was treated with diuretics, digoxin ACEI and antibiotics and discharged after the resolution of symptoms of acute heart failure. She was counselled for corrective cardiac surgery outside Nigeria but could not afford the cost. She remained regular with follow-up on furosemide, digoxin and warfarin until when she relocated with her family to north-western Nigeria and was, therefore, subsequently lost to follow-up.

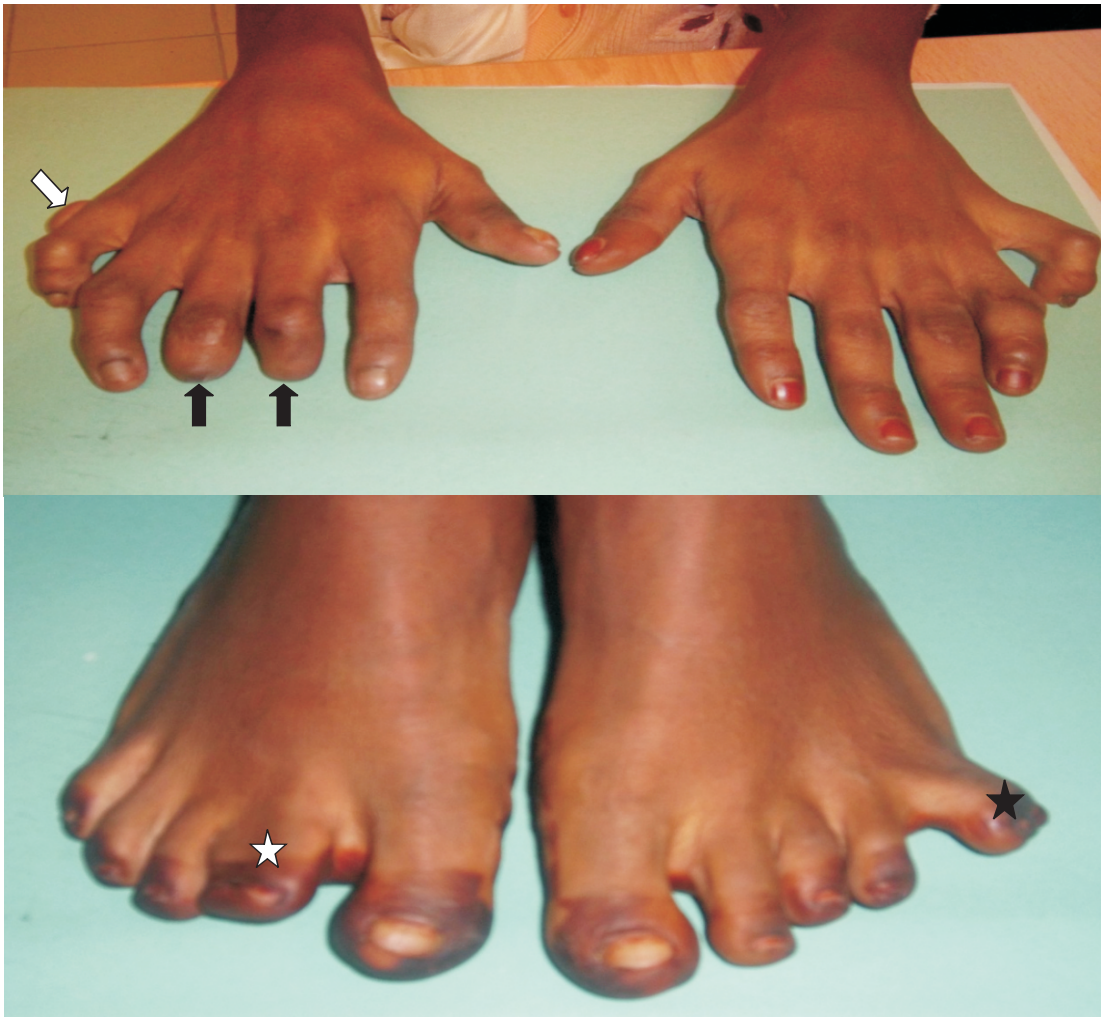

Figure 1: Photographs of both hands and feet showing six digits with a seventh hypoplastic one attached to the sixth, post-axially, on the right hand (white arrow). The 3rd and 4th digits on the right hand are shorter than the remaining digits and have hypoplastic nails (black arrows). The left hand has six well developed digits. The feet demonstrated five digits in the right foot with fusion of the 2nd and 3rd proximal phalanges (white star). The left foot also showed five digits with the 5th digit appearing broader and having two nails (black star).

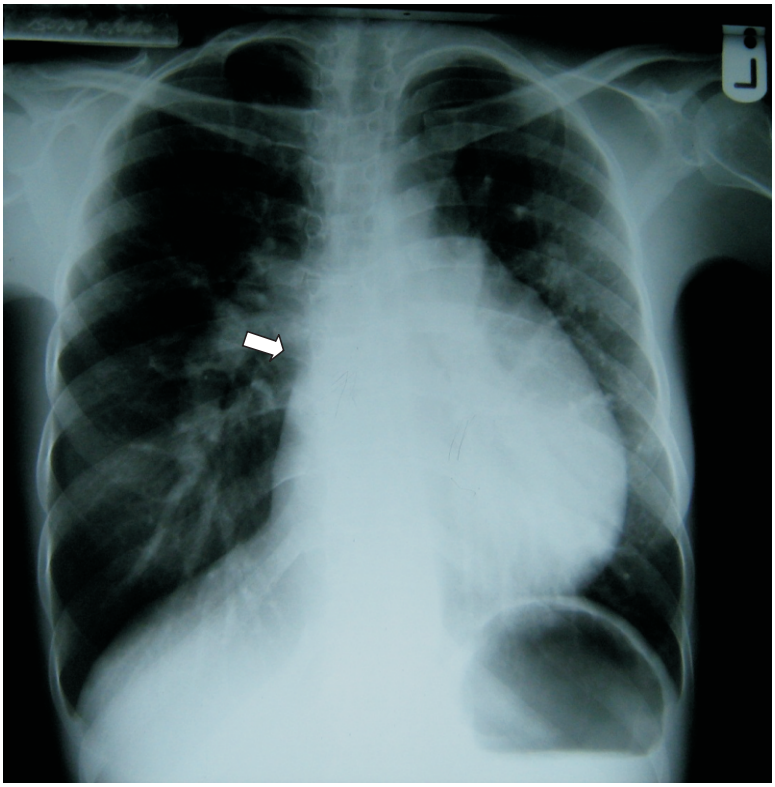

Figure 2: Postero-anterior chest radiograph showing cardiomegaly with rounding of the cardiac apex. Note prominence of the right pulmonary trunk (white arrow).

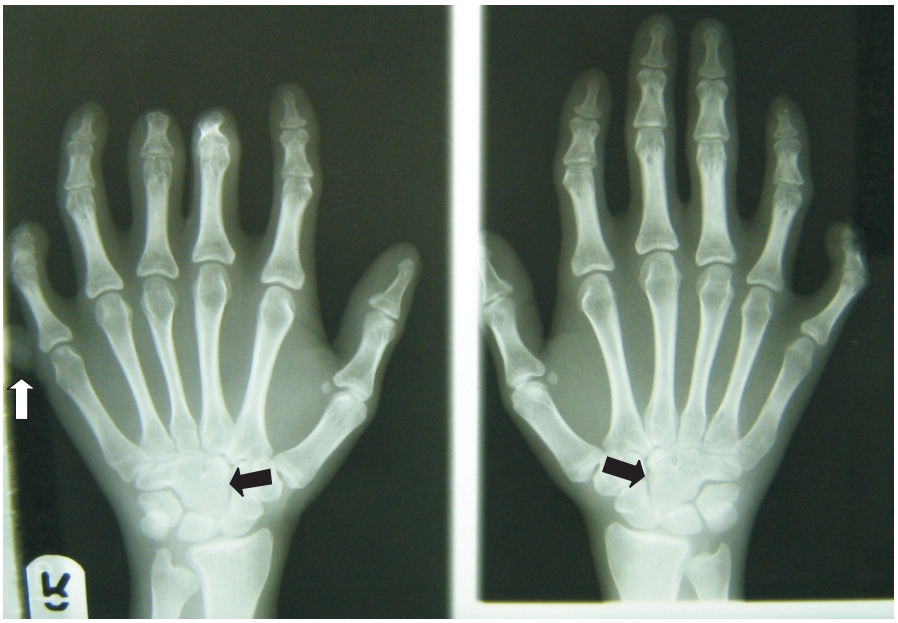

Figure 3: Plain radiographs of the hands showing six digits with a seventh hypoplastic one attached to the sixth, post-axially, on the right hand (white arrow). The middle phalanges in the 3rd and 4th digits on the right are absent. The left hand showed six well developed digits. Note the fusion of the hamate with capitate in both hands (black arrows).

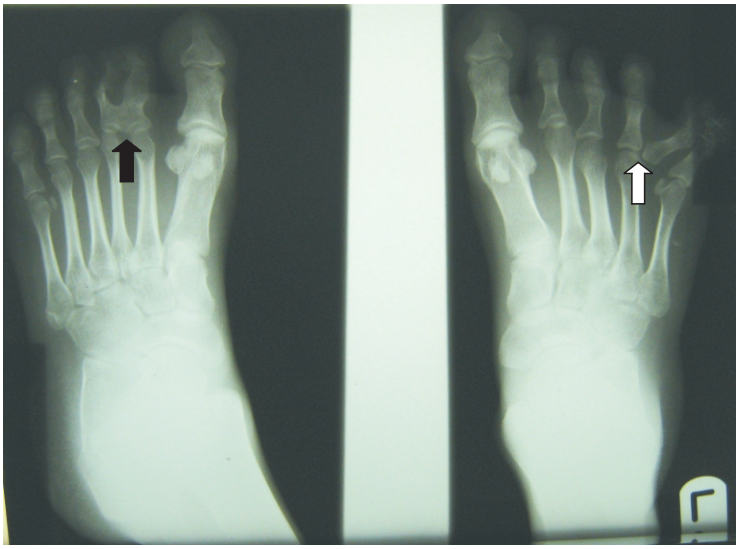

Figure 4: Plain radiographs of the feet demonstrating six digits in the right foot with fusion of the 2nd and 3rd proximal phalanges at their bases (black arrow). The left foot shows five rows of metatarsals with the 4th metatarsal having two proximal phalanges (white arrow).

DISCUSSION

Ellis-van Creveld syndrome is a rare autosomal recessive disorder of skeletal dysplasia associated with cardiac defects and variable phenotypic presentation[2]. Although the syndrome has been partially described in earlier literature, the full description was provided by Richard Ellis and Simon van Creveld in 1940[1]. In most parts of the world, EVC syndrome occurs in 1 of 60 000 to 200 000 live births with almost similar frequency in males and females [3]. It is difficult to estimate the exact prevalence of the disorder because of its rarity. However, it is known that it can affect all races[2,3,4]. The largest pedigree of EVC syndrome has been described in one particular inbred population, the old order Amish community in Lancaster County, Pennsylvania in the United States of America[1]. There is no report of its occurrence in the Nigerian population.

The manifestations of EVC syndrome is quite variable spanning across multiple organs and systems. Some features can manifest prenatally after the eighteenth week of gestation. These include narrow thorax, shortening of the long bones, polydactyly and cardiac malformations[3]. Cardinal postnatal features include disproportionate small stature with shortening of the middle and distal phalanges, bilateral (rarely unilateral) postaxial polydactyly of the hands (and occasionally the feet), malformation of the carpal bones, congenital heart defect (atrioventricular canal with common atrium), and hidrotic ectodermal dysplasia affecting the nails, hair and teeth[3,4].The index patient presented with disproportionate small stature, shortening of the 3rd and 4th fingers on the right, bilateral fusion of the hamate with capitate, atrial septal defect, and hypoplastic nails.

Diagnosis of EVC is highly supported by the presence of congenital heart disease, the main determinant of survival. The case being presented has manifested the majority of the phenotic presentations of EVC, including fusion of the carpal bones (hamate and capitates) commonly seen in blacks [4]. Additional features described include renal abnormalities, hypospadias, epispadias, cryptorchidism, strabismus and haematological abnormalities. Head circumference and mental developments are normal in EVC, as is the case in our patient.

Renal and central nervous system anomalies have also been associated with EVC syndrome[5].

The case presented manifested with bilateral hexadactyly, typical of EVC, a hypoplastic seventh digit on the ulnar side of the right hand which differs from other casesreported previously. Similarly, the missing middle phalanges of the third and fourth digits of the right hand have not been reported in majority of cases. Other skeletal features of EVC including knock-knees, cubitus valgus, hypoplasticcubitus and supernumerary carpal bones were not present in our patient.

Congenital cardiac malformations are a cardinal feature of EVC, observed in 50 to 60% of cases [6]. The abnormalities are mainly of the endocardial cushion defect type, with single atrium being the most commonly observed anomaly[7] similar to what we found in our case. Other cardiac anomalies that could exist with EVC include ventricular septal defects, patent ductus arteriosus, atrial septal defects, defects of the mitral and tricuspid valve and hypoplastic left heart syndrome[6]. A cleft was observed in the mitral valve of our patient, resulting in mitral insufficiency. The severe pulmonary hypertension documented (with clinical finding of central cyanosis) led to the high index of suspicion for Eisenmenger syndromes. Although we noted dilatation of the coronary sinus but we did not observe persistent left superior vena cava or other congenital cardiac anomalies. Trans-oesophageal echocardiography, cardiac MRI as well as catheterization were not available in our centre. The delayed diagnosis of the cardiac abnormality may be due to the relative asymptomatic nature of the atrial defect, until recently when it became complicated by pulmonary hypertension and Eisenmenger syndrome.

The polydactyly in our patient is post-axial. She was also devoid of any renal or central nervous system anomalies that were reported in some cases of EVC syndrome. However, positive family history of similar illness was established as her eldest brother died during neonatal period with an illness suggestive of cyanotic congenital heart disease and polydactyly.

Survivors of EVC syndrome have short adult height and suffer from frequent dental problems (including anodontia) but most of them have intelligence in the normal range[5]. Although our patient had short but proportionate stature, she did not present with dental abnormalities and her intelligence level was normal. The clinical diagnosis of EVC syndrome is based on signs and symptoms and supportive radiological findings. However, definitive diagnosis is based on molecular studies involving gene sequencing and mutation analysis[5]. Radiological investigations carried out included plain radiography of the chest and limbs, ultrasonography and echocardiography. Cardiac CT and MRI are also desirable for diagnoses of EVC syndrome[3,4,8,9,10] but were not available in our centre. The plain chest radiograph showed features suggestive of ASD and pulmonary hypertension including cardiomegaly with rounding of the cardiac apex and prominence of the right pulmonary trunk. The assessment of polydactyly and carpal fusion was satisfactory using plain radiography in our patient.

The diagnosis in our patient was purely based on clinical manifestations, radiological findings and echo-proven congenital cardiac anomaly. The findings of polydactyly in other siblings of our patient lay credence to previous reports of polydactyly in relatives of four unrelated EVC families[2]. Because of lack of facilities for genetic analysis, further evaluation in that regard could not be done. Being an autosomal recessive disorder with a Mendelian risk of about 25%, the patient and other family members were counselled appropriately.

Although the diagnosis of EVC syndrome can be made prenatally using ultrasonography, fetal ultrasound is not routinely done in our region. Prenatal diagnosis is based on defects in late trimester including narrow thorax, postaxial polydactyly, short and bowed long bones, rounded metaphyses and cardiac malformations. Molecular and genetic studies could be conducted using chorionic villus sampling. Our patient, however, did not have any of these prenatal investigations done.

The management of patients with EVC syndrome requires comprehensive multidisciplinary care involving many specialists including diagnostic and interventional radiologist, orthopaedic surgeon, cardiologists, pulmonologists, dentists and occupational therapists[3]. Treatment is mainly symptomatic for the cardio-respiratory problems. Surgical intervention may be required to correct orthopaedic malformations (especially polydactyly) and cardiac defects (percutaneous or surgical closure of the ASD, VSD or PDA)[3,4,6,10]. The cardiac anomaly was detected lately with Eisenmenger syndrome, which may possibly preclude any correction of the defect. She has been referred to a centre where further evaluation and treatment could be offered, but couldn't travel because of financial constraints.

The essential postnatal differential diagnoses of EVC syndrome include McKusick-Kaufman syndrome, Jeune dystrophy and Weyers syndrome[4,6]. Postaxial polydactyly and cardiac defects are observed in both EVC and McKusick-Kaufman syndrome. However, EVC is commonly associated with osteochondrodysplasia and ectodermal anomalies while hydrometrocolpos is present in McKusick-Kaufman syndrome. The presence of cardiac defects, polydactyly and ectodermal anomalies favours the diagnosis of EVC over Jeune dystrophy. In addition, patients with Ellis-van Creveld syndrome, Holt-Oram syndrome and Goldenhar's syndrome present with polydactyly associated with congenital cardiac defects[6]. However, the polydactyly in Holt-Oram syndrome is pre-axial and is usually associated with hypoplasia of the thumb[8]. Goldenhar's syndrome (also known as oculo-auriculovertebral syndrome) is associated with visual and auditory/ear abnormalities in addition to the hemifacialmicrosomia and vertebral abnormalities. The inheritance in Goldenhar's syndrome is autosomal dominant[6].

The prognosis in EVC syndrome is determined by respiratory difficulties related to thoracic abnormalities and cardiac defects[4]. Our patient did not manifest disproportionate thoracic abnormality. However, with the development of Eisenmenger syndrome, the prognosis will largely be determined by the cardiac pathology.

CONCLUSION

The diagnosis of EVC syndrome can be quite challenging, requiring a multidisciplinary approach. Though largely described in the old order Amish community, the occurrence of this disorder has been described worldwide. The presentation of this case in a Nigerian woman further added credence to this assertion of its worldwide occurrence.

REFERENCES

1. Ellis RW, van Creveld S. A Syndrome Characterized by Ectodermal Dysplasia, Polydactyly, Chondrodysplasia and Congenital MorbisCordis: A Report of Three Cases. Arch Dis Child 1940; 15:65-84.

2. Sumit M, Amita T, Veena D. Ellis-van Creveld Syndrome: Report of Two Cases. World J Pediatr 2011; 7(4):368-370.

3. Chakraborty PP, Bandyopadhyay D, Mandal SK, Subhasis RC. A Rare Variant of Ellis van Creveld Syndrome. Singapore Med J 2007; 48(7):684-686.

4. Amaka CO and Christine MH. Skeletal Radiology in Children: Non-traumatic and Non-malignant. In: Grainger & Allison's Diagnostic Radiology, 5th edition. Churchill Livingstone 2008. Pp 1572-1573.

5. Hoffman JI, Kaplan S, Liberthson RR. Prevalence of Congenital Heart Disease. Am Heart J 2004; 147(3):425-439.

6. Peter R, Ruth G. Congenital Skeletal Anomalies; Skeletal Dysplasias; Chromosomal Disorders. In: David S. A Textbook of Radiology and Imaging. 7th edition. Churchill Livingstone, Edinburgh. 2003. Pp 1108-1109.

7. Ferenzc C, Loffredo CA, Correa-Villasenor A, Wilson PD, eds (1997). Atrial Septal Defect. In: Genetic and Environmental Risk Factors of Major Cardiovascular Malformations. The Baltimore-Washington Infant Study 1981-89. Armonk, NY. Fuytura Publishing Co., Inc. Pp 267-283.

8. Moguilevsky HC, O'Reilly MV, Dizadji H, Shaffer AB. Atrial Septal Defect Associated with Skeletal Anomalies (Holt-Oram Syndrome). Chest 1970; 57:230-233.

9. Stoll C, Alembik Y, Roth MP, Dott B, De-Geeter B. Evaluation of Prenatal Diagnosis of Congenital Heart Disease. PrenatDiagn 1993; 13:453-461.

10. Scurlock D, Osler D, Nguyen A, Wahed A. Ellis van Creveld Syndrome and Dyserythropoiesis. Arch Pathol Lab Med 2005; 129:680-682.

Cite this article as: Ahmadu MS, Talle MA, Ahidjo A, Tahir AA
Ellis-van Creveld Syndrome In A Nigerian Woman: A Case Study Bo Med J 2016; 13(1):77 - 84.
Source of Support: Nil, **Conflict of Interest:** None declared.