Case Report

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Double aneuploidy in a 2-month-old male with Edward syndrome and Klinefelter syndrome: a case report

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Introduction and importance: Edward syndrome is a severe chromosomal defect that occurs as a result of non-disjunction through meiosis. It presents with cardiac septal defects, horseshoe kidneys, patent ductus arteriosus, central nervous system dysgenesis, distinctive craniofacial deformities, and overriding or overlapping fingers. Klinefelter syndrome (47, XXY) is found in 1 in 660 newborn males. It is considered to be one of the most common genetic causes of infertility. It manifests with small firm testes, androgen insufficiency, and azoospermia.

Case presentation: A 2-month-old male infant with a history of weakness in feeding, frequent convulsions, and an increase in cyanosis two days ago. There were multiple skeletal deformities and a tendency to spasm in the extremities, left ventricular atrophy, mitral atresia, atrial septal defect, ventricular septal defect with dilated right cavities, tricuspid valve regurgitation, pulmonary valve stenosis; and the aorta exits in the right ventricle. There is a widening of the subdural space, which was observed in the left frontal-parietal side with cortical atrophy in that area and a widening of the Sylvian fissure. A karyotype test confirmed the presence of Edward and Klinefelter syndromes.

Clinical discussion: Aneuploidy is a chromosomal issue characterized by an abnormal number of a chromosome copies. The coexistence of two aneuploidies is called "double aneuploidy" which is a rare occurrence. Herein, we report a case of a 2-month-old male with Edward syndrome and Klinefelter syndrome.

Conclusion: This publication aims to highlight the challenges in diagnosing and treating a complicated genetic disease.

Keywords: case report, double aneuploidy, edward syndrome, klinefelter syndrome, trisomy 18 syndrome

Background

The coexistence of two chromosomal abnormalities in the same person is a rare occurrence and much more common is the occurrence of a double aneuploidy, as in the case of Edward syndrome (ES) and Klinefelter syndrome (KS)[1]. The majority of double aneuploidy cases that have been recorded have resulted in spontaneous abortions[2]. ES is a severe chromosomal defect that usually occurs as a result of non-disjunction through meiosis and affects roughly 0.8 out of every 10 000 babies born alive. The long arm of chromosome 18 from q11.2 has been postulated as the essential region for the trisomy 18 phenotype, while some studies have hypothesized the presence of two essential regions along the long arm of chromosome 18. Cardiac septal defects, horseshoe kidneys, patent ductus arteriosus, central nervous system dysgenesis, distinctive craniofacial deformities, and overriding or overlapping fingers are among the manifestations of the syndrome[3,4]. However, there is no definitive treatment option for ES. The related defects are treated symptomatically; including a nasogastric tube for feeding management, diuretics, digoxin for heart failure or surgical intervention for heart defects,

HIGHLIGHTS

- The coexistence of two chromosomal abnormalities in the same person is a rare condition.
- Most double aneuploidy cases result in spontaneous abortions.
- The diagnosis and treatment process of Edward and Klinefelter syndromes is still challenging.
- The prognosis could be improved by developing new protocols in the diagnosis and treatment process.
- Further research is required to emphasize the correlation between these syndromes.

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Table 1

Describes the laboratory findings

HCO3	Calcium	WBCs	PO2	PCO2	PH	PLT	MCV	HB	Urea	Creatinine
24 meq/l	7.5 mg/dl	7900 cells/mm^3	72 KPa	23 KPa	7.63	279 per liter	94 fl	11.4 g/dl	1.6 mg/dl	0.6 mg/dl

HB, haemoglobin; MCV, mean corpuscular volume; PLT, platelet count test; WBCs, white blood cells.

orthopaedic surgery for scoliosis, seizure medication, and finally treatment of associated infections and respiratory problems. The differential diagnosis for ES is relatively wide: Pena-Shokeir syndrome type I, distal arthrogryposis type I with joint contractures, and CHARGE syndrome (coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities)[5]. The foetus's prognosis after delivery is poor, with just about 8% surviving for one year[3]. KS (47, XXY) is the most common chromosome aberration (found in 1 in 660 newborn males) and is considered to be one of the most common genetic causes of infertility (found in 3% of infertile males and 11% of azoospermic males). The existence of a sex chromosome aneuploidy has many organ implications for the patient. Small firm testes, androgen insufficiency, and azoospermia are all manifestations of KS[6]. When these two syndromes coexist, the clinical features of ES predominate, and it is difficult to diagnose KS clinically without karyotyping[1,7]. Before the birth of the foetus, the diagnosis is confirmed by both amniocentesis and cordocentesis, in addition to many other prenatal sonographic findings that are associated with these syndromes[2]. Testosterone replacement therapy is the most commonly used medical treatment for KS. However, the side effects of this treatment have not been well evaluated, and additional research is required to assess its implications on metabolic risk and neurocognitive outcomes[8]. The main differential diagnosis for KS is Kallmann syndrome[9]. Although many people with sex chromosome mutations can live normal lives, others may have psychological, developmental, physical, behavioural, or learning problems[6]. We report a 2-month-old male infant with ES along with KS. This case report has been reported in line with the SCARE criteria[10].

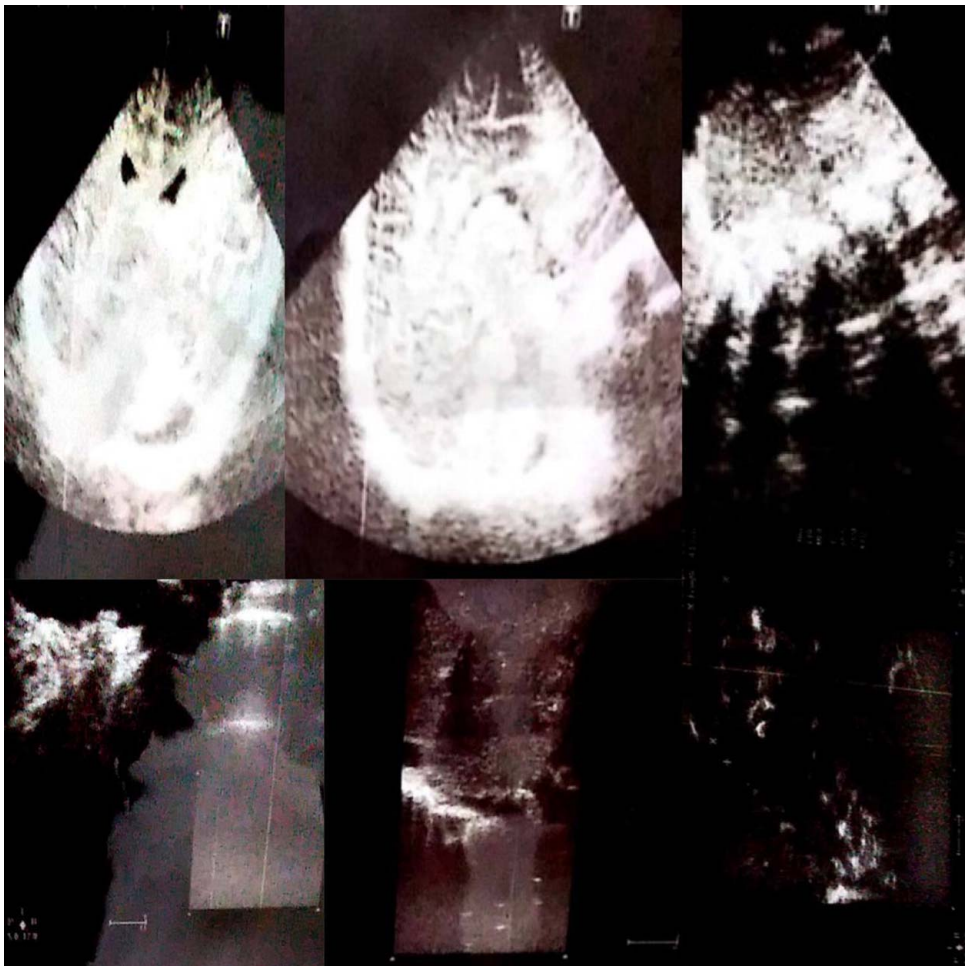

Figure 1. The presence of left ventricular atrophy, mitral atresia, secondary atrial septal defect with the left-right ventricular flow in it, presence of ventricular septal defect with dilated right cavities, tricuspid valve regurgitation, right ventricular systolic pressure of 65 mm, and aorta exists in the right ventricle.

Case presentation

A 2-month-old male presented to the Emergency Department with a history of weakness in feeding, frequent convulsions, and an increase in cyanosis 2 days ago. No familial or medical history was reported. The clinical examination revealed multiple skeletal deformities (low-set ears with adhesion in the left ear to the head, retraction in the lower jaw, bilateral talipes equinovarus, and the presence of a special mien). In addition to the presence of subcostal, substernal, and intercostal retractions, there were fine rales in both lungs that referred to pneumonia. The abdomen was soft, all four sides were cold, there was a bilateral direct inguinal hernia, and the testicles were palpable. The nervous system examination revealed a tendency to spasm in the extremities. Sensation, muscle tone, and skin reflexes were within normal limits. The patient had intrauterine growth restriction before

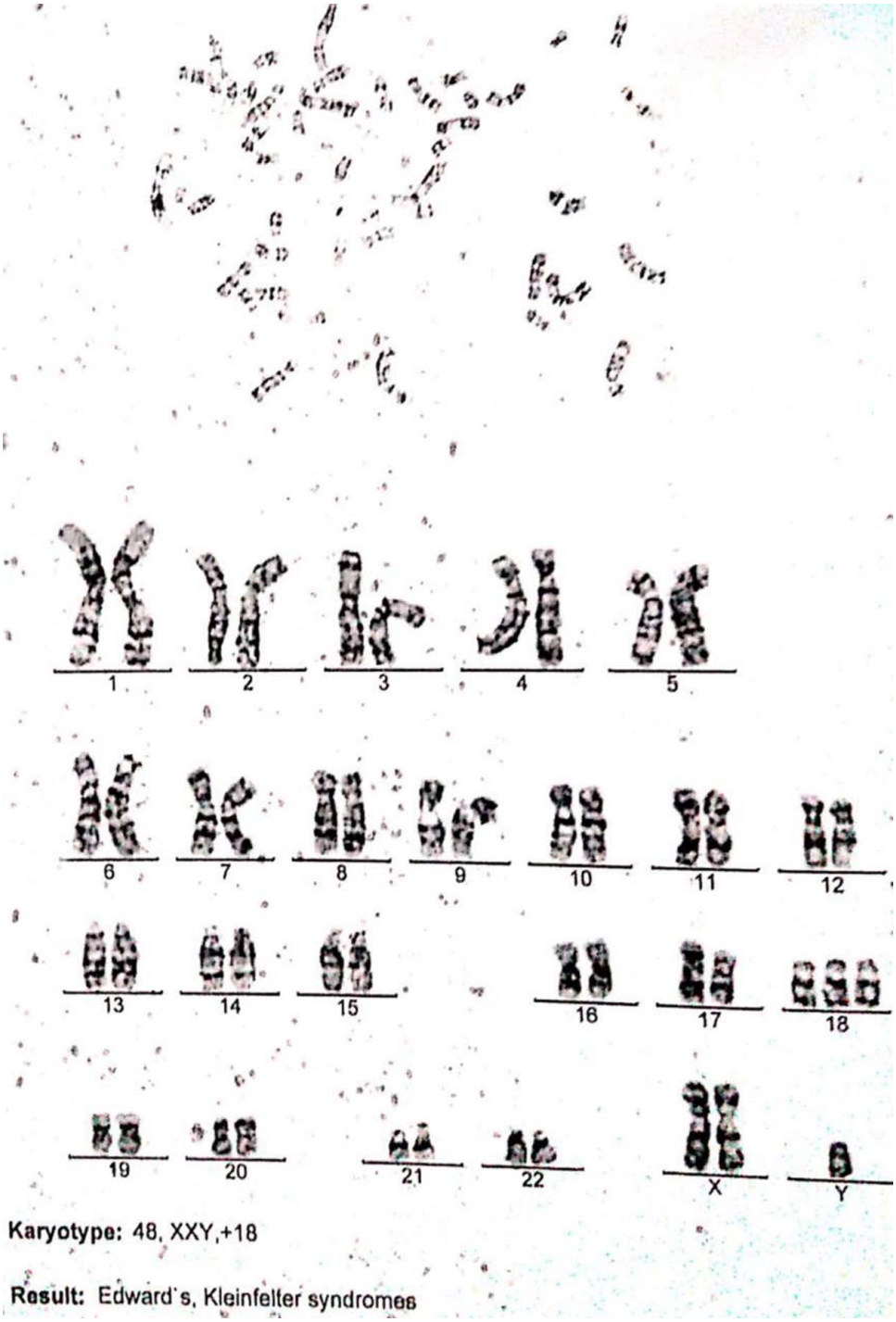

Figure 2. Karyotype demonstrated 48 XXY, + 18.

Table 2

The characteristics and management of double aneuploidy (48, XXY, +18).

Reference	Pt age (years)/ sex	Paternal age (years)	Pregnancy	Measurements	Patients karyotype	Clinical examination	Diagnostic tests	Findings	Surgical management (rationale)
Hou *et al.*[2]	Newborn/M		39 week-foetal distress	BW: 2040 g, Body Length: 49cm, HC: 29.5 cm 15M: BW: 3.8 kg, Length: 73cm, HC: 37.2 cm	48, XXY, +18	Severe psychomotor retardation, IUGR, poor weight gain, microcephalym N height, cryptorchidism, N penis, prominent occiput with long skull, dysplastic ear, hypertelorism, broad nasal bridge, small nose small mouth, micrognathia, high-arched palate, short sternum, single umbilical artery, diaphragmatic hernia, clenched hands, overlapping fingers, rocker-bottom feet, scoliosis, clinodactyly limited hip abduction, hypoplastic scrotum.	Echo, Kidneys US, hearing test, visual evoked potential stimulation, FISH, EEG, Blood tests	Echo: PDA, VSD, PS 15m: T4, T3, TSH blood levels N Radiological studies: mild cardiomegaly, scoliosis of thoraco-lumbar spine and a small narrow pelvis 15M: echo: Atrial septal defect (3.7 mm), VSD (10 mm) PA banding with distal migration (Vmax 3.9 m/s). Kidneys US: left kidney hypoplasia atrophy with right kidney hydronephrosis. Hearing test by brainstem auditory evoked potential: abnormal. Visual evoked potential stimulation N FISH: No mosaicism EEG: Mildly diffuse cortical dysfunction. No abnormal epileptiform discharges. Hemogram, electrolytes, blood glucose, metabolic screening N	Emergency surgery to repair hernia. 2m: Ligation of PDA + PA banding. 15m: Tracheostomy, mechanical ventilation.
Vaniawa *et al.*[7]	7 days/M	Mother: 30 Father: 32	Normal gestation and delivery	NA	48, XXY, +18 /46, XY	Dysplastic low-set ear, microcephaly, micrognathia, cleanched hands with broad fingers.			
Chen *et al.*[12]	22 weeks Foetus/M	Mother: 42 Father: 43	Ended at 22 weeks	Termination at 22 weeks, 332 g	48, XXY, +18	Facial dysmorphism, low-set ears, hypertelorism, rocker-bottom feet, Micrognathia, Arthrogryposis of left wrist, Aplasia of left thumb, clenched hands, N penis	Prenatal US, Ameniocentesis	Prenatal US At 18 weeks: choroid plexus cysts. At 22 weeks: a flexion contracture deformity of left wrist, absence of left thumb. Amniocentesis: 48, XXY, +18	
Cohen *et al.*[13]	Newborn/M	Mother: 21 Father: 35	Delivery at 40 weeks	Body Length: 47 cm, HC: 34.5 cm, BW: 2670 g 1M: BW: 2184 g Body Length: 48.1 cm	48, XXY, +18	facial dysmorphism, micrognathia, clenched hands, rocker-bottom feet, normal male genitalia, undescended testes, clinodactyly, prominent occiput, hypertelorism, palpable liver, poor hand grip and gag reflex	X-ray, Fluoroscopic examination, ECG	X-ray: middle phalanx absence, rudimentary phalanges of both little fingers, absent first metacarpal of left thumb, radial deviation of both hands. Bilateral forefoot inversion, no definite ossification centres of middle and distal phalanges Fluoroscopic examination: grossly enlarged heart with dominant right ventricle, acyanotic congenital heart disease, possible total	At 6-week: Neonatal death

								anomalous venous drainage, single atrium or single ventricle. ECG: right ventricular hypertrophy	
Zellweger *et al.*[14] Case 1	Newborn/M	Mother: 23 Father: 29	Delivery at 43 weeks	At birth: BW: 2070 g 17 days old: BW:1800 g HC: 31 cm Body length: 47 cm	48, XXY, +18	high-arched palate, facial dysmorphism, micrognathia, clenched hands, short sternum, congenital heart failure, cardiomegaly, hepatomegaly, hypertonic and hypoplastic muscles, dorsiflexed and short big toe.	Radiological examination Intravenous pyelograms ECG postmortem examination Histological examination of gonads	Radiological examination: cardiomegaly,short sternum, very thin ribs, dislocation of right hip. Intravenous pyelograms:N. ECG: atrioventricular block Postmortem examination: ventricular septal defect, patent ductus arteriosus, Meckel's diverticulum. Histological examination of gonads: infantile structure of testicular tubules	At 10-week: Neonatal death
Henchman *et al.*[15]	Newborn-1month/ M	Mother: 23 Father: 26	Delivery at 40 weeks	BW: 2140 g	47, XXY/ 48, XXY +18	wide-set eyes w/folds beneath, small and pursed mouth, broad chest, clinodactyly, facial dysmorphism, micrognathia, clenched hands, grade 1 systolic murmur	ECG Radiograph Postmortem examination	ECG: newborn: N 2.5 months: right ventricular hypertrophy Radiograph: considerably enlarged heart shadow, increased pulmonary vascular markings, thin and malformed rib, small and poorly formed first metacarpal, maldevelopment of middle and terminal phalanges of all toes. Postmortem examination: ventricular septal defect, patent ductus arteriosus,enlargement of right kidney	At 3-month: neonatal death
Sørensen *et al.*[16]	21 h/M	Mother: 42 Father: 50	Delivery at 41 weeks	BW: 2000 g Body Length: 44.5 cm HC: 34.5 cm	48, XXY, +18	syndactyly, facial dysmorphism, micrognathia, clenched hands, congenital diaphragmatic hernia, dilated renal tubules, large square fontanelle, bird-like face,sunken nasal bridge, antimongoloid slanting of eyes, small and pointed mouth, low-set and slightly deformed ears, low hair level, tendency to webbing of neck on left side.short, high-frequency blowing systolic murmur.	Autopsy	Autopsy: left-sided posterior diaphragmatic hernia, hypertrophic heart, ventricular septal defect, kidneys microcysts, aplastic corpus callosum absent septum pellucidum and fornical system, double central canal in cervical part	At 21 h: neonatal death
van Ravenswaaij-Arts *et al.*[17]	Newborn\M	Mother: 26 Father: NA	Delivery at 38 weeks,	BW: 1746 g HC: 31 cm Body length: 41.5 cm	47, XY, +3/ 48, XXY, +18.	hypertelorism, blepharophimosis, bilateral cleft lip and palate, micropenis, cryptorchidism, ventriculomegaly, camptodactyly, hypoplasia of cerebellar vermis, facial	Prenatal US Amniocentesis US EEG	Prenatal US at 31 weeks: IUGR, polyhydramnios, bilateral cleft lip. Amniocentesis: 47, XY, +3/ 48, XXY, +18. US:	At 10 days: neonatal death

Table 2

(Continued)

Reference	Pt age (years)/ sex	Paternal age (years)	Pregnancy	Measurements	Patients karyotype	Clinical examination	Diagnostic tests	Findings	Surgical management (rationale)
						dysmorphism, clenched hands, low-set malformed ears.		atrioventricular septal defect. EEG: dilated ventricle	
Begam *et al.*[18]	NewbornM	NA	NA	NA	48, XXY, + 18	Facial dysmorphism, clenched hands	Prenatal US Amniocentesis	Prenatal US at 34 weeks: IUGR, choroid plexus cysts, strawberry shaped head cerebellar hypoplasia, ventricular septal defect, club feet, clinodactyly, pectus excavatum. Amniocentesis: 48, XXY, + 18.	At 2 days: neonatal death

BW, body weight; ECG, electrocardiogram; Echo, echocardiogram; EEG, electroencephalogram; F, female; FISH, fluorescence in situ hybridization; HC, head circumference; IUGR, intrauterine growth restriction; M, male; N, normal; PA, pulmonary artery; PDA, patent ductus arteriosus; PS, pulmonary stenosis; Pt, patient; TSH, thyroid stimulating hormone; US, ultrasound; VSD, ventricular septal defect.

birth. The vital signs revealed a heart rate of 140–150 per min, a respiratory rate of 40–50 per min, and no fever. Laboratory tests were performed and the results are listed in Table 1 [Table1]. An echocardiogram demonstrated the presence of left ventricular atrophy, mitral atresia, a secondary atrial septal defect with an 8 mm diameter with the left-right ventricular flow in it, a 7 mm in diameter ventricular septal defect with dilated right cavities, tricuspid valve regurgitation, right ventricular systolic pressure of 65 mm, the aorta exits in the right ventricle, and a pulmonary valve stenosis pressure of 30 mm [Fig. 1]. The abdominal echography revealed irregular and thickening of the inferior posterior wall of the bladder. A bone X-ray was normal. The scrotal echography is not clear due to the presence of severe gas shadows within the intestinal lumen. Brain sonography suspected intraventricular haemorrhage. Following that, a cranial computed tomography without injection revealed a widening of the subdural space, which was observed in the left frontal-parietal side with cortical atrophy in that area and a widening of the Sylvian fissure. The thickening of the cerebral cortex was noted in the right parietal lobe, which raises the possibility of migration defects. Finally, the golden test was a karyotype that was diagnosed as having a rare and odd coincidence; the patient had ES and KS [Fig. 2]. The patient was placed on mechanical ventilation and treated conservatively with phenobarbital due to convulsions, but the patient eventually died. The patient's parents had no special concerns about the management process.

Discussion

Aneuploidy is defined as the occurrence of an abnormal number of copies of a particular chromosome. Double aneuploidy occurs when two aneuploidies involving two different chromosomes coexist in a single individual. Double autosomal syndrome, which can be formed by a combination of two autosomes (48 + 18 + 21, 48 + 13 + 21, 48 + 13 + 18) or a sex chromosome and an autosome (48 XXY + 21, 48 XYY + 18, 46 × 0 + 21), is unusual in live newborns[1,7]. ES (Trisomy 18 syndrome) is far less common in live births than Down Syndrome (Trisomy 21) and Patau syndrome (Trisomy 13). The second-most frequent multiple malformation is trisomy 18, with a female-to-male ratio of 3:1[2,7]. KS (47, XXY) affects about one in every 650 males and is one of the most common genetic causes of infertility. However, there is still no accurate definition of KS. According to epidemiological studies, only about 25% of adult males with KS are ever diagnosed, and diagnosis is rarely made before puberty[6,8]. A mosaic double aneuploidy of chromosome 18 and sex chromosome X (48 XXY + 18) causes ES and KS to coexist, with a total of 16 cases having been reported worldwide. To our knowledge, this is the first time that ES and KS have been reported combined in one case in Syria. As in our case, the majority of patients with ES are diagnosed at birth since they display the particular trait of trisomy 18 and, in certain studies, clinical symptoms of ES were found to be prominent when two diseases coexisted[11]. The pregnancy was uneventful except for intrauterine growth restriction in our case as well as in 14 other patients with ES and KS, with maternal ages ranging from 21 to 45 years[11]. The typical features of Trisomy 18 include congenital heart malformations, diaphragmatic hernia, prominent occiput, "rocker-bottom" feet, low-set ears, micrognathia, overlapping fingers, and the characteristics of KS cryptorchidism

and long thin limbs were apparent in the other cases[1,2,7,11]. Our patient had certain ES characteristics, such as low-set ears, bilateral Talipes equinovarus, which was only found in one other case[12], and congenital heart malformation [Fig. 1], but no KS features. The testicles were palpable, and the upper and lower extremities were likewise normal. Aside from the characteristic signs of ES and KS, which are difficult to detect clinically, the karyotype test is the gold standard for all cases, including our case [Fig. 2]. Congenital cardiac defects, such as ventricular septal defect and patent ductus arteriosus, which account for more than 90% of Trisomy 18 patients, make it challenging for these patients to live a long life[1,2]. Other than the congenital heart anomaly that resulted in heart failure, our patient also had kidney failure and a neurological defect that resulted in intraventricular haemorrhage. The patient was placed on mechanical ventilation and the complications were managed conservatively. The vast majority of these pregnancies end in miscarriage. In one study, double aneuploidies were found in 2.18% of miscarriages[1]. Within the first year, 50% of trisomy 18 patients die as they develop serious deficits[2]. Four of the cases died within one week of birth; three of the cases died between the ages of 10 and 18 days; six of the cases died between the ages of 1 and 4 months, and one case survived for over 21 months[11]. Many cases experienced poor outcomes, including early mortality and a significant number of cases experienced severe complications, such as feeding difficulties, recurrent infections, heart failure, and severe failure to thrive[1,2]. Unfortunately, our patient died at the age of 2 months due to severe complications [Table 2].

Conclusion

We present this case due to the rarity of live deliveries with the stated abnormality, highlighting the importance of developing a new protocol to improve the prognosis of such syndromes. We may better understand these illnesses and the lives of those impacted by them by further research and collaboration among scientists, physicians, and advocacy organizations.

Ethical approval

Ethics approval is not required for case reports at our institution. Institution name: Damascus University Children Hospital, Damascus, Syrian Arab Republic.

Consent

A consent was obtained from the patient parent for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Author contribution

All authors read and approved the final manuscript. M.M.: design of the study and table, data collection, data interpretation and analysis, drafting, critical revision, and the approval of the final manuscript. A.A.: data collection, data interpretation and analysis, drafting, critical revision, and the approval of the final manuscript. S.Z.: design of the table, data collection, data interpretation and analysis, drafting, critical revision, and the approval of the final manuscript. G.A.: data collection, drafting, critical revision, and the approval of the final manuscript. R.M.: data collection, drafting, critical revision, and the approval of the final manuscript. N.K.: data collection, drafting, critical revision, and the approval of the final manuscript. Y.A.: data collection, drafting, critical revision, and the approval of the final manuscript. R.A.: patient care, drafting, critical revision, and the approval of the final manuscript. A.M.D.: preparing correspondence files, preparing the final manuscript, approval of the final manuscript. M.A.: the supervisor, patient care, drafting, critical revision, and the approval of the final manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

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Data availability statement

Not applicable. All patient data generated during this study are included in this published article and its supplementary information files.

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