ABSTRACT Introduction: Ellis-van Creveld syndrome is known as chondroectodermal dysplasia or mesoectodermal dysplasia. It is a rare genetic disorder with autosomal recessive inheritance resulting from these patients’ malformations.

Case Report: A repetitive syndrome is reported in the present article. Pregnant woman with a fetus with Ellis-van Creveld syndrome is described with a rare concomitant abnormal findings of Dandy-Walker malformation. The aim is to emphasize the importance of the ultrasound differentiation of prenatal diagnosis in patients who have fetuses with congenital anomalies. A 26-year-old pregnant woman was diagnosed with a fetus with congenital anomaly Ellis-van Creveld Syndrome associated with Dandy-Walker malformation. In her history of diseases, previously she has had three indicated abortions due to central nervous system and limbs deformities. She has only one healthy child. The patient was examined clinically, paraclinical, digitally, and has had genetic examinations performed on her, her partner, and fetus. The patient prenatally was diagnosed with caring a fetus with shortening of the long bones, thoracic dysplasia, hexadactyly of the hand, arterial septal defect in addition to Ellis-van Creveld accompanied by Dandy-Walker syndrome. From the results obtained it has been deducted that the pregnancy needs to be terminated.

Conclusion: A multidisciplinary approach is needed in prenatal diagnosis and family genetic counselling for the wellbeing of a fetus and the entire family.

KEYWORDS Ellis-van Creveld syndrome, prenatal diagnosis, genetic counselling

Background
Ellis-van Creveld syndrome is an autosomal recessive ciliary lesion associated with a wide range of abnormalities of the ectoderm, skeletal system, and heart. [1] It was first discovered by Richard WB Ellis of Edinburgh, Scotland, and Simon van Creveld of Amsterdam, the Netherlands, in 1940, and is named after its distinctive genotypic and phenotypic characteristics. It is a rare genetic disorder where the basic feature is skeletal dysplasia, which includes the presence of the sixth finger of the hand, dwarf growth according to Subash Singh [2] who described this condition as “six-fingered dwarfism”. It has been studied primarily among the Amish, in their population, specifically in Lancaster County, Pennsylvania, in the United States of America, due to the rarer mixing of the genotype. Four features characterize Ellis–van Creveld syndrome: 1) disproportionate dwarf growth with short rib arches and markedly narrow and elongated thorax; 2) postaxial polydactyly of the arms, pronounced bilaterally, and/or deviations in the upper and lower extremities, 3) dental pathologies, such as hypodontia or malformed teeth 4) congenital cardiomyopathy with a frequency of up to 66% of cases with confirmed presence of the syndrome. Less commonly described clinical features are cryptorchidism, epispadias, palatoschisis, hypoplasia of the distal phalanges, or dystrophic nails. [3] The
EVC gene has been described as being located on the short distal arm of chromosome 4p16. Identified genes such as EVC1 (MIM # 604831) and EVC2 (MIM # 607261) are discovered to be responsible for the inherited genetic material. The syndrome is caused by a defect in one of the two genes for Ellis-van Creveld syndrome (EVC1 and EVC2) next to each other at the chromosome 4p16, in an area proximal to other chondrodystrophy. They both share common promoter region [3] A mutation in these genes has been identified in the Amish population. Screening for 21 EVC coding exons in 58 patients with EVC, enabled the identification of only 13 patients with homozygous mutations. In the remaining 45 cases, no mutation in one or both alleles has been verified. The most accurate verification is achieved by analysis of cDNA of the fibroblast and its RNA, although in those results that are usually the syndrome is not excluded but is described as a probability of genetic heterogeneity. The second gene, EVC2, located next to the previous gene, is placed in a head-to-head configuration. This gene (166.4 kb) is expressed in the heart, placenta, lungs, liver, and skeletal muscle. The transcriptional beginnings of both genes are separated by only 1643 bp. [4] There is no significant sequential homology at the protein level and at the nuclear level. The EVC2 gene encodes a protein with a single transmembrane segment and one RhoGEF domain (SMART). Mutation of the so-called The LIMBIN gene (bovine orthologue of EVC2) is associated with chondrodysplastic dwarfism. The EVC2 protein has a significant homologous sequence at the end where class IX of nonmuscular myosin (BLAST) is located. Affected individuals with mutations in both genes are phenotypically recognizable. [5] According to McKusick [6], in a study of 52 cases of children from 30 pairs of parents have been described. The second most frequently found place is in the population of Western Australia. Nowadays, it has been established that it is a syndrome that occurs in every race or population. By 2007, about 150 cases had been verified, and until 2019, about 200 cases, since the syndrome was discovered and described in the literature. In the world population, the incidence ranges from 1 in 60,000 to 1 in 200,000 newborns. In contrast, in the Amish population, the incidence is the percentage that is 1 case per 200 live births. In this population, the frequency of gene carriers for this syndrome is 13%. [6] According to Vinay, however, it is a very rare syndrome with a prevalence of 7 per 1000,000 live births. [7]

Case report
A repetitive syndrome is reported in the present article. Pregnant woman with a fetus with Ellis-van Creveld syndrome is described with a rare concomitant abnormal findings of Dandy-Walker malformation. The aim is to emphasize the importance of the ultrasound differentiation of prenatal diagnosis in patients who have fetuses with congenital anomalies.

A 26-year-old patient with sixth pregnancy came in the University Clinic of Gynecology and Obstetrics in Skopje, Republic of North Macedonia. She had her initial examination at 21.5 gestational weeks. The patient was given a questionnaire for the history of diseases, for previous pregnancies, and for other comorbidities. She was examined in detail. Her anamnestic data had discovered that her first pregnancy ended with abortion. In that pregnancy in 2013, due to ultrasound findings in the screening of the second trimester in 21 week, cist of the cerebellum and short limbs were diagnosed. MRI had been made for verification of the diagnosis, and because of an explanation for a
poor prognostic outcome for the fetus, termination of the pregnancy was indicated. She had a second successful pregnancy in 2014, delivery with a healthy male child 3400 grams. After that followed 2 indicated abortions in the second trimester of pregnancy, her pregnancy in the year 2015, also ended in induced abortion at 21.3 gestational weeks due to proven Ellis van Creveld syndrome at the Lipp Clinic, in Steinstein, Germany. In 2016, she had had another pregnancy terminated in 22 weeks of gestation at the University Clinic in Skopje. The ultrasound findings on the second-trimester screening confirmed enlarged cisterna magna(1.7mm), absence of vermix of the cerebellum, enlarged third ventricle of the brain, hypoplastic nasal bone (7.1mm), heart defect (absent atrial septum, hypoplasia of left heart ventricle, enlarged right ventricle, undefined LVOT and RVOT), shortening of upper and lower extremities (corresponding to17 gestational age both, femur and humerus). One year after, she had had an artificial abortion in 8 gestational weeks pregnant. In this pregnancy, in February 2020, screening for fetal anomalies was performed. Amniotic fluid was collected and send for karyotype analysis. After signed consent for terminating the pregnancy, induction was performed. X-ray of the fetus was performed. The fetus and the placenta sent to the Institute of Pathology and histology for autopsy. Material for genetic analyses was collected from the gluteal muscle of the fetus and sent in MANU for confirming the gene corresponding to Ellis-van Creveld syndrome.

Discussion

From the used materials and methods, important information was obtained from the situation of the patient. It had been discovered that there was no consanguinity among both partners. In this pregnancy, the patient underwent an ultrasound examination at 21.5 weeks of gestation (screening in the second trimester). In the ultrasound examination, shortening of the upper and lower extremities was diagnosed (humerus and ulna correspond to 17.5 (bellow percentile) and 15.4 (<1%) gestational age respectively, tibia and fibula to 17.5 (<1%) and 16.3 (<1%) gestational age respectively). Also on the palm of the fetus hexadactyly was found, narrow chest, absence of cerebellum vermix and posterior cranial fossa in addition to Dandy-Walker syndrome. The ultrasound findings are demonstrated in figures 1-5 because of these findings that indicate bad prognostic outcome, the pregnancy needed to be terminated. Misoprostol-induced termination of the pregnancy was indicated in the patient.

The findings after delivery of the fetus confirmed the ultrasound examination, where shortened limbs, right-hand hexadactyly, narrow thorax, and head deformities were verified after fetal expulsion. (Figures 6-9) An X-ray of the fetus was taken, so that complete diagnosis can be obtained. (Figure 10) For genetic confirmation of the syndrome, a sample of the gluteal muscle was taken for genetic detection of fibromyoblast. The fetus and the placenta were also sent for autopsy. The autopsy material confirmed the diagnosis of a male fetus 400 grams
weight and 26 cm long in support of hexadactyly (polydactilia mani lateris dextri). Atrial septal defect of 0.4 cm was found, short limbs, absence of vermix in the cerebellum and posterior cranial fossa with conical shape in support of Dandy-Walker. From the genetic analysis of the amniotic fluid analyzed 4800 clinically significant genes, by using Tri Sight One kit, Illumina and bioanalyses of the genome, and no genetic disorder for a male fetus was confirmed from this test, but, the fibroblast result was inconclusive which did not exclude the Ellis-van Creveld syndrome.

The presented case shows accurate diagnosis of prenatally ultrasound diagnosed shortening of the long bones, thoracic dysplasia, hexadactyly of the hand, arterial septal defect in addition to Ellis -van Creveld accompanied by Dandy-Walker. Based on the previous result from the Hospital in Germany, the same diagnosis was confirmed according to the ultrasound findings of the fetus in this pregnancy that describe clinically Ellis-van Creveld syndrome. The X-ray confirmed the ultrasound findings of the skeletal system. The performed amniotic chariot is not a sensitive method for confirming this syndrome.

Authors have discovered that in the first trimester, there is an ultrasound association with an increase in the thickness of the nuchal translucency with EvC syndrome. In cases where recurrence occurs, prenatal diagnosis to verify the syndrome is possible with chorionic biopsy. [8] In the second trimester, the diagnosis can be confirmed based on positive family history and ultrasound-confirmed shortening of the upper and lower extremities, hexadactyly of the arms, narrow chest, short ribs, and congenital cardiac defects. [9]

Sund and colleagues [10] found that EvC expression and EvC mRNA and the increased presence of proteins in the circulating and mesenchymal protrusion are also present in the mesenchymal structure of the atrial septum and are responsible for cardiac defects.

When pathogenesis for the occurrence of Ellis-van Creveld has been studied, it was concluded that according to Mendeleev’s law it is inherited autosomal recessively with a recurrence risk of one in four, or 25% for each pregnancy from both same parents. Although it is most common in the Amish, there is no racial or gender predisposition. Consanguinity is present in 30% of confirmed cases.

Ellis-van Creveld belongs to the SRP group [11] (short rib syndrome and polydactyly, a heterogeneous group of autosomal recessively inherited skeletal dysplasias). Differentially diagnostic include SRPs, type I (Saldino Noonan-deformed limbs, polydactyly polycystic kidneys and enlarged metaphysis), type II (Majerski-polydactyly, micromelia, palatoschisis, polycystic kidney, short tibia and hypoplastic epiglottis and larynx), type III (Verma-Naumoff syndrome-polydactyly, micromelia, metaphyseal deformities and situs inversus totalis). Jeune asphyxia thoracic dystrophy [12] is characterized by thoracic dystrophy, chondrodysplasia, short ribs, short, long bones, damage to the acetabulum and damage of the liver, retina, and kidneys. In contrast, McKusick-Kaufman syndrome is characterized by post-syngae polydactyly and clindodactyly. [13]

McKusick-Kaufman syndrome is caused by mutations in a gene on chromosome 20p12, encoding a protein similar to members of the chaperonin family. [14] In the autosomal dominant condition heart defect, thoracic dysplasia and disproportionate dwarfism are not present.

In intrauterine fetuses where Ellis-van Creveld syndrome has been found with high probability and certainty, termination of that pregnancy is indicated due to the uncertain outcome regarding perinatal and neonatal morbidity and mortality that is dependent on the narrow chest and the presence of cardiomyopathy.
Histopathological verification of the syndrome is confirmed by chondrocyte disorganization in the growth zone in the cartilage of the long bones of fetuses. Chondrocyte disorganization is then confirmed in the vertebrae, in the central physiological zone of growth. [15]

If pregnancy is not terminated, life expectancy is uncertain and dependent on respiratory comorbidities due to deformed thorax and congenital heart defects. About one-third to one-half die in the early infantile period. Early diagnosis and a multidisciplinary approach are most important for further coping with cardiorespiratory complications. With no other comorbidities present, after surviving complications in early childhood, a normal survival period is expected (the oldest case is an 82-year-old man) [16]. However, the history of the neonatal period includes anamnestic data on fetuses small for gestational age, slower growth, and skeletal malformations present. In all cases where the syndrome is confirmed, hexadactyly of short and wide palms is present.

Congenital cardiac malformations are found in 50 to 60% of cases. They include a single atrium, occluded ductus arteriosus, mitral and tricuspid valve defects, ventricular septal defects, atrial septal defects, and hypoplastic left heart syndrome. Significant difficulties in neonates manifest as a cardiac murmur, hunger for air, cyanosis, and other cardinal signs of cardiac arrest. [17] The presence of disproportionate and dwarf growth is present, and the shortening of the body’s limbs is visible. Short stature and polydactyly are characteristic features and functionally limitation or inability of the wrist or performing fine motor tasks are expected [15].

The nails are hypoplastic, brittle or dystrophic, from thin or oval to completely absent. In hair, eyebrows and pubis, the hairs are brittle and thin. Manifestations of the oral region are numerous and involve the fusion of the middle portion of the upper lip with the maxillary gingival region, in the absence of normal mucosal sulcus. Natal or neonatal teeth and congenital absence of teeth, especially on the mandible, are common. The growth of new teeth is delayed, i.e. partial anodontia is present.

Conclusion
A multidisciplinary approach is needed in confirming the condition of a fetus with Ellis-van Creveld accompanied by Dandy-Walker syndrome. Prenatal ultrasound identification of skeletal system changes, cardiac defects, and central nervous system abnormalities can confirm the syndrome. Thus necessitates genetic testing for Ellis-van Creveld syndrome and family genetic counselling.

Further studies are needed to elucidate other genes involved

Figure 9 Head deformities.

Figure 10 X-ray of the fetus.

A larger percentage of surviving patients do not have deviations in the central nervous system and intelligence. However, in a smaller percentage, there persists mental retardation and abnormalities present of the CNS. Case reports have cited patients with associated brain malformations (Dandy-Walker anomaly, hydrocephalus, cerebral heterotopias) and developmental delay. Two have been shown in 2018 and one in 2019 cases of Dandy-Walker syndrome together with Ellis-van Creveld syndrome. [19] Also, there are finding Dandy walker syndrome associated with Ellis-van Creveld syndrome. This case report showed the first case in the Republic of North Macedonia of Ellis-van Creveld with Dandy-Walker malformation.

Parallel comorbidities can lead to severe organ damage, including renal - nephrotic syndrome, nephronophthisis and renal failure, hepatic impairment due to congenital biliary obstruction, leading to progressive fibrosis, and hepatic, renal failure. Myelodysplastic changes to dyserythropoietic to acute leukaemia. [20, 21]
in EvC manifestations. They could also contribute to unraveling specific molecular processes that lead to the phenotypic manifestations of EvC.

Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

References


