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BRIEF COMMUNICATION

Unusual Clinical History of a Male Infant with Edwards Syndrome

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Abstract Edwards syndrome (trisomy of chromosome 18) is generally characterized by the disorders of central nervous system, as well as the musculoskeletal and genitourinary systems. In majority of the cases with trisomy 18 the following malformations can be found: ventricular septal defect, horseshoe kidneys, oesophageal atresia, omphalocele, facial clefts, diaphragmatic hernias and genital hypoplasia. We report a male patient with Edwards syndrome. The boy had a partial agenesis of corpus callosum, oesophageal atresia with tracheo-oesophageal fistula, renal agenesis, ventricular septal defect, Dandy-Walker cyst and low-set malformed ears. The first three features are unique based on previous literature reports on trisomy 18. This report allows a further delineation of the trisomy 18 syndrome.

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Abbreviations

ACC	agenesis of corpus callosum
p-ACC	partial agenesis of corpus callosum
CNS	central nervous system
GI	gastrointestinal
GU	genitourinary
NODCC	National Organization for Disorders of the Corpus Callosum
US	ultrasound
VSD	ventricular septal defect

Introduction

Organ systems such as CNS, musculoskeletal and genitourinary systems are mostly affected in Edwards syndrome. Agenesis of the corpus callosum is a rare congenital anomaly in Edwards syndrome, while this syndrome is frequently associated with other craniofacial and skeletal abnormalities. The incidence of corpus callosum agenesia is increased in patients with chromosomal abnormality. Several familial cases have been reported so far [1–7].

Spectrum of Abnormalities

Corpus Callosum Developmental Defect

ACC can be complete, partial or atypical. With complete agenesis the corpus callosum is totally absent. It is in 75% of the cases [8]. With partial agenesis (dysgenesis), the anterior portion (posterior genu and anterior body) is

formed, but the posterior portion (posterior body and splenium) is not formed. The rostrum and the anterior/inferior genu are also not formed, as in our case. They represent about 30% of corpus callosum abnormalities [8, 9]. An atypical appearance occurs when the anterior to posterior formation is not respected.

Frequency of Abnormalities

In ACC the frequencies of some of the most commonly associated anomalies are as follows:

- CNS anomalies (85%)
- Cardiovascular, GI and GU anomalies (62%)
- Hydrocephalus (30%)
- Dandy–Walker cyst (11%)
- Arnold–Chiari malformation (7%)

The reported frequency of ACC is 0.7–5.3% [10]. However some researchers suggest as many as seven in 1,000 children may have agenesis of the corpus callosum, while others believe it may be as rare as five in 1 million [11]. In Hungary the CNS system defects appear less frequently. The occurrence of overall CNS abnormalities is 1.819‰ based on 95,317 live births. The corpus callosum defects form 0.01‰ of the cases [12].

Agenesis of the corpus callosum has many genetic causes [13]. An autosomal recessive form was characterized by Jonas RE et al. (1993) [14] who reported an affected brother and sister. ACC is reported to be more common in males than in females as like Edwards syndrome [10]. ACC is a congenital or a developmental anomaly, and therefore, is present at the time of birth. In many cases, agenesis is diagnosed later in infancy or in childhood due to the associated congenital malformations [10]. Agenesis of corpus callosum may be of syndromic or non-syndromic type. The most common form is the one not associated with any syndrome [15].

Development and Anatomy

Fibers of the corpus callosum arise from the superficial layers of the cerebral cortex and they project to the homotypic region of the contralateral cortex by passing through the corpus callosum while crossing the midline. Disturbance of embryogenesis in the first trimester of gestation by some unknown insult leads to failure of the callosal axons to pass across the midline. These arrested axons form the longitudinally oriented bundles of Probst that are located medial to the lateral ventricles in patients with agenesis [10]. The corpus callosum develops from the lamina reuniens in the telencephalon, and it begins to appear between the anterior and hippocampal commissures at about 10.5 week. In a typical fetal brain, the corpus callosum develops between 12 and 16 weeks after conception, near the end of the first trimester. The adult form of the corpus callosum is achieved by the 17th week of gestational age. Initial formation of the corpus callosum takes place in the genu and the body, progressing posteriorly. The anterior genu and rostrum develops at last, folding back under the genu. The callosum thickens with increasing myelination [11, 16].

According to the National Organization for Disorders of the Corpus Callosum (NODCC), most patients are diagnosed within the first 2 years of life. The disruption to the development of the corpus callosum occurs during the 5th to 16th weeks of pregnancy. There has been no single cause identified. A review of the embryology of the corpus callosum suggests that several different mechanisms can result in ACC. Furthermore, ACC is not a single malformation or a malformation spectrum.

Many different factors can interfere with the development such as:

- Prenatal infections or viruses such as rubella, influenza
- Genetic factors are probably predominant. Autosomal dominant, autosomal recessive and sex-linked transmission have all been documented [6]. In addition, ACC has been reported in more than 20 autosomal malformation syndromes [1–7, 10, 11, 13, 14, 17, 18]
- Toxic metabolic conditions such as fetal alcohol syndrome, valproate, cocaine [6]
- Blockage of the growth of the corpus callosum by cysts [6].

When corpus callosum is absent, the third ventricle is often high riding, extending superiorly between the lateral ventricles. On coronal imaging, a candelabra appearance occurs, with the third ventricle forming the central vertical portion and with the lateral ventricles forming the peripheral arms of the candelabra. On axial imaging, the lateral ventricles are parallel.

Associated midline cysts are noted in some cases. The exact origin and nature of these cysts is controversial. While some of these cysts represent a dilated superiorly migrated third ventricle, others represent true midline cysts that may be lined by ependymal cells or by arachnoid membranes [10].

Antenatal diagnosis of ACC is possible from about the 20th week of gestation. Characteristic intrauterine ultrasound (US) findings include colpocephaly and parallel ventricular walls. CT findings are also diagnostic of ACC. Parallel lateral ventricles, colpocephaly, and extension of the third ventricle into the interhemispheric fissure are particularly pertinent findings. In patients with ACC and an interhemispheric cyst, the preoperative injection of non-ionic water-soluble contrast material into the cystic loculations for CT enables assessment of the ventricular system or

of the communication of the cystic components with one another [10].

A distinction should be made between complete and partial agenesis of the corpus callosum. Complete agenesis of the corpus callosum is commonly regarded as a malformation, deriving from faulty embryogenesis, while partial agenesis of the corpus callosum may inform about a disruptive event occurring at any time during pregnancy [17].

Degree of Confidence Ultrasound examination, especially transvaginal US, helps in the prenatal diagnosis of non-chromosomal syndromes by enabling the detection of specific morphological findings. In rare syndromes, the index case may not be prenatally diagnosed, but subsequent pregnancies may benefit from early diagnosis. However, MRI has been seen to be more helpful in the prenatal diagnosis of corpus callosum dysgenesis [10].

More than three-quarters of the cases belong to complete agenesia, while the rest is considered as partial agenesia. The complete cases can be evaluated by US in utero. The frontal lobe/biparietal diameter ratio were determined in fetuses with corpus callosum agenesis. In the presence of classic ultrasonographic features of the agenesis of corpus callosum, frontal lobe shortening, along with absence of the cavum septi pellucidi, might contribute to the diagnosis of complete agenesis of corpus callosum distinguishing it from partial agenesis [8].

Dandy–Walker Cyst

Dandy–Walker syndrome is a congenital brain malformation involving the cerebellum and the fluid filled spaces around it. The main conditions of the syndrome are an enlargement of the fourth ventricle, a partial or complete absence of the cerebellar vermis and cyst formation near the internal base of the skull, called arachnoid cysts. These cysts may develop between the surface of the brain and the cranial base. Small cysts are usually asymptomatic while larger cysts may cause cranial deformations, headaches, seizures, hydrocephalus and increased intracranial pressure [11].

In Hungary the rate of congenital brain cysts is 0.15‰, and Dandy–Walker cysts are responsible only for a part of them (0.01‰) [12].

Genitourinary Abnormalities

An increased association with genitourinary abnormalities has been previously defined in Edwards syndrome. Renal anomalies were the most frequent genitourinary abnormalities identified in these children, although ureteral, genital and bladder abnormalities were also encountered. There was an exceptionally high incidence of undescended testes (23%), approximately 20-fold greater than the frequency in the normal population, possibly resulting from hypothalamic insufficiency associated with midline cranial defects. Therefore it is suggested that all patients should be thoroughly evaluated with bladder and renal ultrasound studies to rule out any genitourinary abnormalities. Male patients with agenesis of the corpus callosum and undescended testes should undergo hypothalamic/pituitary axis testing [19]. In Hungary the rate of genitourinary abnormalities is 9.9‰, while the rate of renal agenesia is 0.06‰ [12].

Oesophageal Atresia and /or Tracheo-oesophageal Fistula

Chromosome alterations are associated with oesophageal atresia in up to 10% of the cases. Chromosome 18 trisomy was detected in about 1% of the affected children [20].

In Hungary the frequency of oesophageal defects is 0.13‰ [12].

There were no patients who had major cardiac anomalies or trisomy 18 in total 24 patients with congenital oesophageal atresia in a Japanese 28-year retrospective study [21] and only one of the deaths (2.5%) was associated with severe anomaly that was incompatible with life in another study [22].

Two reports analyzed the associated anomalies in infants with variants of oesophageal atresia and/or tracheo-oesophageal fistula. Associated anomalies occurred in 64% of infants, including cardiovascular defects in 28% and 38%, skeletal defects in 12% and 19%, neurological defects in 15%, genitourinary abnormalities in 8% and 15%, other gastrointestinal defects in 8% and 17%, and other congenital lesions abnormalities in 13% and 16% including even trisomy 18 [23, 24].

Materials and Methods

A 34-year-old woman (gravid 3, bipara) underwent an ultrasound examination. We investigated the pregnancy at the 30th week of gestation. The pregnant woman visited our department because of polyhydramnios and a possible oesophageal atresia. The patient's medical history did not contain any pathological antecedents. Family history did not comprise neural tube defects, hydrocephalus nor any other congenital neurological abnormalities. The patient denied to have consumed alcohol, drug, tobacco or any other toxic substances. We confirmed the diagnoses of polyhydramnios and oesophageal atresia and besides we found further malformations of the fetus during detailed ultrasound screening made with the help of SonoAce 8000 (Medison) ultrasound equipment fitted with 3–5 MHz transabdominal transducer.

Results

Findings in coronal brain sonograms included the following:

Partial Agenesis of Corpus Callosum (p-ACC) (1) Ventricular enlargement at the level of the occipital horns, resulting in a teardrop configuration of the lateral ventricles, (2) an enlarged and upwardly displaced third ventricle, the third ventricle has been displaced upward and can be seen at the same level as the bodies of lateral ventricles, (3) the midline echo has become a three line complex due to distension of the interhemispheric fissure, (4) absent septum pellucidum, (5) elongation of the interventricular foramen of Monroe. The brain gave an indication of p-ACC. The genu and anterior body of corpus callosum could be seen, while the posterior body, splenium, and rostrum were hidden. The frontal lobe/biparietal diameter ratio was in normal range (81%, normal is 74–85% at 30th week of gestation) [8].

Dandy–Walker Cyst All the typical signs of a Dandy–Walker cyst (enlargement of the fourth ventricle, partial absence of the cerebellar vermis and cyst formation near the internal base of the skull) could be observed.

The ultrasound screening showed renal agenesia, structural heart defects, low-set malformed ears and a special form of fingers (Figs. 1a, 2 and 3) in addition to oesophageal atresia. The typical ultrasound signs of a chromosomal defect, especially Edwards syndrome did not manifest themselves. We sought for undescended testicles, omphalocele, diaphragmatic hernias, protuberance of the occipital bone, microcephaly, micrognathia, small mouth, cleft lip/palate, occular hypertelorism, overlapped, flexed fingers and clubfoot in vain. The ultrasound investigation was repeated by another ultrasound specialist as well. The patient was then referred to the Department of Paediatrics and Paediatric Surgery. We asked for cardiologic and surgical consultation in order to confirm diagnosis (e.g. ventricular septal defect and oesophageal atresia) and to determine the chance of survival. The malformed ears, Dandy–Walker cyst, polyhydramnios and growth retardation raised the issue of genetic disorder, but it was irrelevant at the 30th week of gestation. The pregnancy was terminated because of fetal dystress by Caesarean section at the 38th week of gestation. The birth weight was 1,680 g. Apgar scores were 4, 7 and 8 at first, fifth and tenth minutes. After birth the neonate was transferred to the Department of Paediatric Surgery for repairing oesophageal atresia. In the operation theatre the surgeons noticed the tracheo-oesophageal fistula as well. Following the operation the infant needed intensive therapy. The cardiac malformation, such as VSD was confirmed again and no other anatomical malformation in the heart was revealed. The neonate had special form of fingers called hammer fingers, however the toes were normal. The Department of Perinatal Intensive Care Unit asked for a chromosomal analysis. At the Department of Paediatrics Edwards syndrome was described with atypical clinical signs. The neonate died in consequence of pneumonia at the 28th day of his life. Autopsy unveiled partial corpus callosum agenesia (Fig. 4a and b), an operated oesophageal atresia with a tracheo-oesophageal fistula, renal agenesis on the right side, VSD (Fig. 1b) and a Dandy–Walker cyst.

Discussion

In Edwards syndrome the phenotype ranges from asymptomatic cases with normal intellectual capacity to severe mental retardation. Radiological and genetic markers cannot make a difference between the asymptomatic and symptomatic characteristics of the disease. Therefore, it is

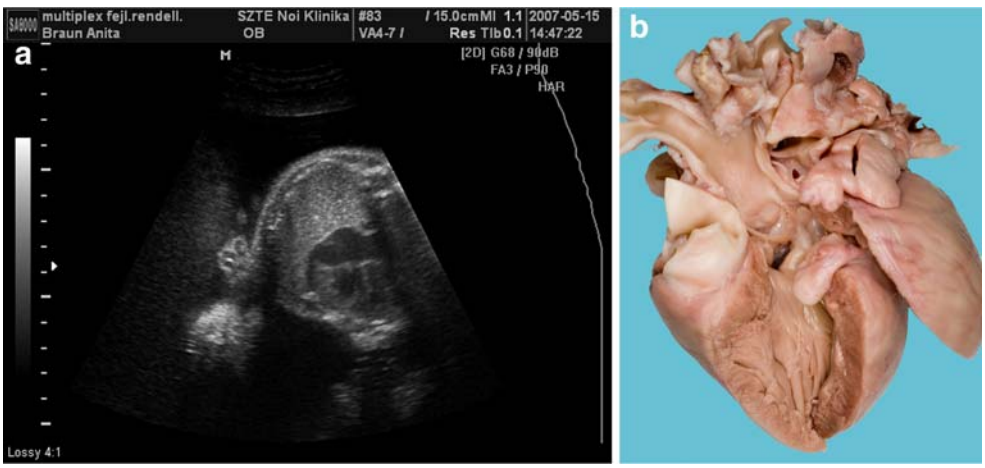

Fig. 1 **a** Congenital heart defect. Prenatal ultrasound picture. **b** Ventricular septal defect. Dissection photo

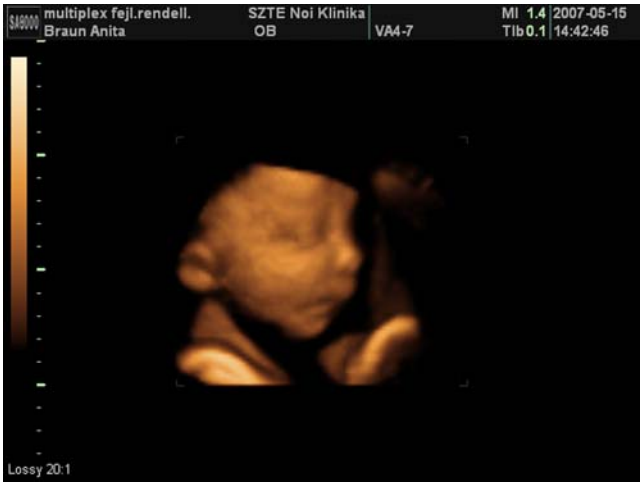

Fig. 2 Low-set, malformed ears. Prenatal ultrasound picture

very difficult to give genetic advice if the diagnosis is made during prenatal care.

In 97% of the cases with trisomy 18 three or more malformations can be found: (VSD 67%, horseshoe kidneys 32%, oesophageal atresia 11%, omphalocele 14%, facial clefts 14%, diaphragmatic hernias 11% and genital hypoplasia in more than 50%) [25].

We analyzed the data of National Centre on Birth Defects and Developmental Disabilities Centres for Disease Control and Prevention, Hungary. Twenty-eighth cases of Edwards syndrome were diagnosed in 2004 and 64% of them had a detailed preliminary prenatal diagnosis as well [12].

In and of itself, the corpus callosum is not essential for life or health—or even for a productive intellectual life. The use of patients with acallosal defects have identified mutations in at least thirty genes of the human genome with roles implicated in the development of the corpus callosum. Patients with chromosome aberrations have been useful in defining regions on chromosomes that contain

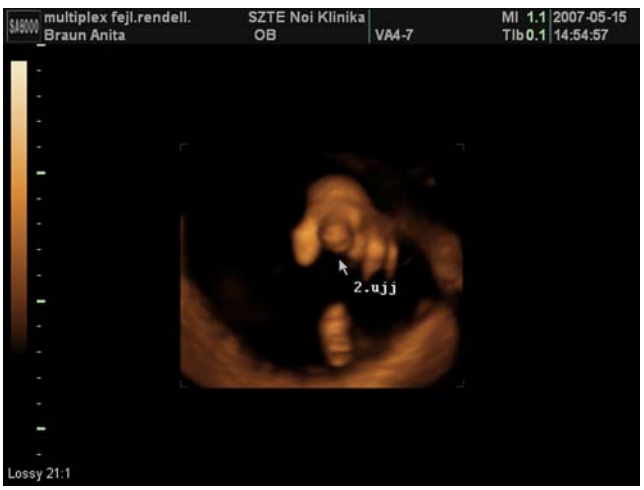

Fig. 3 Special form of fingers. Prenatal ultrasound picture

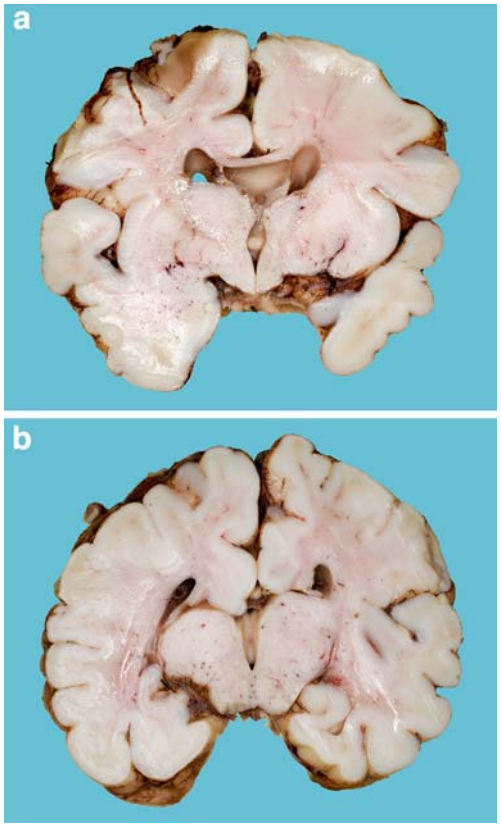

Fig. 4 **a** Partial agenesis of the corpus callosum at the level of the anterior commisure the well-formed callosum. Dissection photo. **b** Partial agenesis of the corpus callosum at the midthalamic level the callosum is discontinuous. Dissection photo

candidate genes for the development of the corpus callosum. At least 18 different human chromosomes with numerical and/or structural aberrations have been reported in patients with acallosal defects [26]. The partial corpus callosum agenesia is a very complex matter, because this problem is partly a disturbed embriogenesis around of 12–16th weeks of gestation because of genetic and/or toxic factors, intrauterin infection or the involvement of a mechanical defect with cysts, hamartomas or lipomas [16].

The natural history of partial agenesis of the corpus callosum is nevertheless uncertain, and the cerebral findings associated with it are probably more subtle than with the complete form. It is expected that antenatal diagnosis will not be possible in all cases. However, it is expected that by including the cavum septi pellucidi among the intracranial structures routinely visualized most cases with complete agenesis of the corpus callosum should be detected. It should be kept in mind however that visualization of the cavum septi pellucidi is usually possible only after 18 weeks' gestation [8, 9, 17, 27, 28].

In our report we present a new clinical manifestation of Edwards syndrome namely the partial agenesis of corpus callosum combined with rarely occurring malformations such as oesophagial atresia.

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