



# A Rare Case Report of Edwards Syndrome with Immature Teratoma in Submandibular Region and Literature Review

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## Abstract

Trisomy 18 (Edward syndrome) was first described by Edwards et al. in 1960. The condition is the second most common autosomal trisomy syndrome in males. The prevalence in infants is estimated as 1/6000-1/8000. Those affected have a high mortality rate – only 4% may survive their first year.

The study illustrates the first reported case of Edwards syndrome with immature teratoma in submandibular region.

A 33-year-old multigravida had a normal antenatal course until 36 weeks of gestation. Two hours after delivery, the baby was transported to a neonatal ward, where several malformations were described: a tumour formation the size of a walnut in the right submandibular region, ear abnormality, micrognathia with high arched palate, overlapping fingers, and feet deformities. A genetic test was performed which confirmed trisomy 18. After 26 days of assisted ventilation and oxygen therapy, the newborn developed hyaline-membrane disease, dilatation of the pulmonary artery and the right side of the heart, thrombosis of the right atrium and these conditions were determined to be the cause of death.

The autopsy and histological examination confirmed the aforementioned malformations finding also a kidney with duplicated collecting system on the right and ectopic ureter in the left kidney. The submandibular tumour was determined to be immature teratoma.

**Conclusion:** This is the first presented case in the literature of a newborn with Edwards syndrome combined with immature teratoma.

## Keywords

Edwards syndrome, immature teratoma, trisomy 18, submandibular region

## INTRODUCTION

Edwards syndrome (trisomy 18) is a disease characterised by the presence of an additional copy of chromosome 18, most likely from maternal origin, due to an error in meiotic division. It was first described by Edwards et al. in 1960. The prevalence of the condition varies between 1/6000 and

1/8000 live births but the overall prevalence is thought to be higher as most of these pregnancies end up in miscarriages in the early stages of the pregnancy. Another reason for this is a good perinatal diagnosis leading to termination of these pregnancies. The incidence is higher in girls (3:1).<sup>[1,2]</sup>

Clinically the syndrome manifests itself with multiple

malformations, some of which are life threatening, as well as a higher risk of developing many tumours.

## CASE REPORT

We present a case of Edwards syndrome diagnosed postmortem in 2019 at the Department of Pathology, St George University Hospital, Plovdiv. The presence of Edwards syndrome was confirmed by a genetic test shortly after birth. The child survived for 26 days dying of respiratory distress syndrome as a result of hyaline membrane disease. Autopsy was performed. After a thorough gross examination, representative sections were taken from different organs. The necropsy was fixed in 10% formalin. Sections were processed routinely with paraffin embedding and stained with haematoxylin and eosin (H and E).

### Case history

A 33-year-old multigravida with no history of genetic disorders in previous pregnancies, who had not seen an obstetrician during the pregnancy, was admitted to the Obstetrics and Gynecology Clinic with a ruptured amniotic sac and spontaneous labour. The infant was female, weighing 1800 g,

lobes, micrognathia, high arched palate, pes equinovagis on both feet and the characteristic contractures of the second finger on both hands. The diagnostic imaging found a kidney with duplicated collecting system on the right and an ectopic ureter on the left kidney as well as a rectovaginal fistula.

A genetic test was carried out which proved trisomy 18. The child spent 26 days in intensive care unit in the Pediatric Clinic and died of pneumonia, urinary tract infection, kidney and heart failures.

The autopsy confirmed the described malformations. The tumour formation in the submandibular area at autopsy was well demarcated from the mandible, whitish in colour and homogeneous whitish, slightly cystic cut surface. The tumour was well encapsulated, moderately vascular and showed adhesion to the right submandibular gland. Grossly, the mass measured 5×4 cm with white-tan solid and nodular areas (Fig. 2). Abnormalities of both kidneys were confirmed – a double kidney on the right and an ectopic ureter on the left one (Fig. 3).

No congenital heart anomalies were seen; however, a relative pulmonary valve stenosis led to hypertrophy and dilation of the right side of the heart and a septal thrombosis of the right heart ear. After 26 days of assisted ventilation and oxygen therapy, the newborn developed hyaline-membrane disease, dilation of the pulmonary artery and the right side of the heart with thrombosis of the right atrium; these condi-



**Figure 1.** Tumour formation in the submandibular region /Arrow/. Gross picture.

and born by natural birth. Two hours after delivery, it was transferred to the neonatology ward where several malformations were described: a tumour formation in the submandibular region 5×4 cm in diameter (Fig. 1), malformed ear



**Figure 2.** Grossly, the tumour mass measured 5×4 cm, with white-tan, solid and nodular areas.

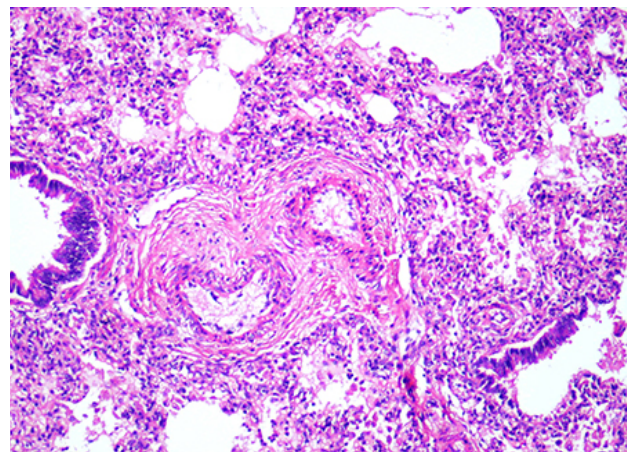


**Figure 3.** The right kidney was found with duplicated collecting system and the left with an ectopic urether.

tions were determined to be the cause of death.

Histological examination showed that as a result of the prolonged oxygen therapy (with an oxygen tent procedure) and assisted ventilation, the infant developed pulmonary hypertension (grade 2, with medial thickening and a small amount of endothelial intimal thickening of the pulmonary blood vessels) (Fig. 4), hyaline-membrane disease, which together with the described heart pathology led to acute right heart failure which is considered to be the immediate cause of death. A diffuse and nodular hyperplasia of the adrenal glands was also seen.

Microscopic examination of the tumour formation determined it to be an immature teratoma presented histologically with immature neuroectodermal tissue. Histologically, the tumour shows chiefly immature neuroepithelial tissue having



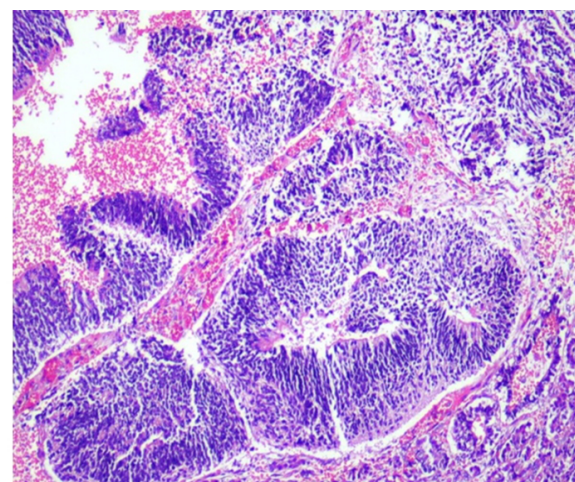
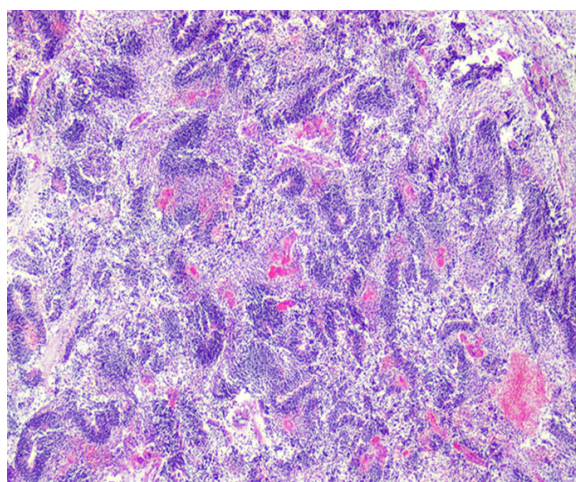
**Figure 4.** Pulmonary hypertension grade 2 with medial thickening and a small amount of the intimal thickening of the pulmonary blood vessels. Original magnification. HE  $\times 10$ .

elongating neuronal cells centred around the neurofibrillar material (Fig. 5) and a small area, in the periphery, represented by bronchial tissue. These features were consistent with grade 2 immature teratoma of the neck.

## DISCUSSION

In 1967, Karunakaran and Pai<sup>[3]</sup> reported the first case of trisomy 18 from India. It was a chromosomal disorder resulting in a syndrome characterized by specific dysmorphic features and organ malformations.<sup>[4]</sup> It is the second most common trisomy after Down syndrome (trisomy 21).

The phenotype of Edwards syndrome results from full, mosaic or partial trisomy 18q. Complete or full trisomy 18



**Figure 5.** Immature neuroepithelial tissue having elongating neuronal cells centred around the neurofibrillar material. Original magnification. HE  $\times 4$ , HE  $\times 10$ .

is the most common form. The extra chromosome is present because of meiotic nondisjunction in 80% of cases, mosaicism in 10%, translocation in 5%, and trisomy 18 plus sex chromosomal aneuploidy in 5%.<sup>[5]</sup> Higher prevalence of methylene tetrahydrofolate reductase gene (MTHFR) polymorphisms in mothers of trisomy 18 fetuses is reported. The recurrence risk for a family with a child with complete trisomy 18 is usually taken to be 1%.<sup>[6]</sup>

No specific risk factors have been described so far, but the mother's age is thought to be relevant.<sup>[7]</sup> Most patients die in the embryonic or fetal stage of their development. The median age of survival among live births varied between 2.5 and 14.5 days.<sup>[8]</sup> Survival beyond one year is rare.<sup>[5,7]</sup>

Live-born children present clinically with multiple malformations of various organs and systems.

Maxillofacial anomalies are low set and deformed ear lobes, microcephaly, micrognathia, cleft lip, and cleft palate. Craniofacial malformations include microcephaly with prominent occiput, narrow bifrontal diameter, short palpebral fissures, low set malformed ears, a cleft lip, a cleft palate, narrow palatal arch, and micrognathia.<sup>[9-11]</sup>

Extremities abnormalities: most common abnormalities associated with extremities are clenched fists, overlapping of fingers, hip abduction defect, nail hypoplasia, and rocker bottom feet, short dorsiflexed big toes, fixed flexion deformity of fingers, simple arch pattern of fingers and toes. Other abnormalities are short sternum, narrow pelvic ring, restricted abduction of the femur, single transverse palmar crease, and simian crease. Skeletal malformations include webbed neck, widely spaced nipples, small pelvis, congenital dislocation of hip, and limited hip abduction.<sup>[9,10]</sup>

Central nervous system: choroid plexus cysts, ventriculomegaly / hydrocephaly; neuronal tube defects; abnormal intracranial anatomy.<sup>[9,12]</sup>

The frequency of congenital heart defects is very high in patients with trisomy 18: greater than 90%.<sup>[8]</sup> They include a ventricular septal defect, atrial septal defect, persistent ductus arteriosus, transposition of the great arteries, Fallot tetralogy, coarctation of aorta, dextrocardia, aberrant subclavian artery, pulmonary stenosis, and bicuspid aortic or pulmonic valves.<sup>[9,13]</sup>

Genitourinary system malformations include cryptorchidism, double ureter, horseshoe kidney, ectopic kidney, hydronephrosis and polycystic kidney disease. Undescended testis is commonly associated with this syndrome.<sup>[9,11,14,15]</sup> In our case, for the first time we describe a kidney related anomaly – right kidney with duplicated collecting system and the kidney with an ectopic ureter.

Other possible malformations are intrauterine fetal growth retardation, umbilical cord anomalies, hydrops, oligo / polyhydramnios, and cystic hygroma.<sup>[12]</sup>

Children born with trisomy 18 also have a higher risk of developing some tumours. It is most commonly hepatoblastoma. The most common histological subtype is highly differentiated or fetal type. Embryonal type or the mixed fetal-embryonal types are less common. The second most common tumours are nephroblastomas. These two types of

tumours account for roughly 5% of the neoplasms in patients with Edwards syndrome. However, other more common pediatric tumours have not been described in newborn with trisomy 18. For example, brain tumours (representing more than 20% of childhood tumours) and leukemias (25% of malignancies in children under 15 years of age).<sup>[16]</sup>

There are heart tumours which despite being called different names – myxoma, valvar hamartoma, papillary tumour or fibrous vegetations, have the same histological image – papillary architecture with loose mesenchyme which has no blood vessels.

Other less common tumours include neuroblastoma, gastrointestinal tract polyps, Hodgkin's disease, adenomas in different organs, nodular hyperplasia of the adrenal gland, proliferating hamartomatous lesions as well as mature teratomas.<sup>[16]</sup>

The tumour formation we described in our case was an immature teratoma, localized in the right submandibular region next to the submandibular salivary gland.

Teratomas are tumours consisting of heterogenous cells or organ-like structures arising from all three embryonal layers. There has been no proof of a connection between gender and tumour growth. The most common localization is the sacrococcygeal region, but they can arise anywhere along the body median line. Those who arise in the head and neck are quite rare and account for 3% of all localizations. While less common, they still arise along the median line of the body – medial in the neck, nasopharynx, thyroid gland, infratemporal fossa. The more common histological type is mature teratomas.<sup>[17-19]</sup>

Immature teratomas of the head and neck represent a small percentage of all teratomas with that localization. Most neck teratomas are reported as mature, and malignant immature teratomas have been said to occur in approximately 5% of teratomas of the neck. Macroscopically, they can be solid, cystic or mixed type. In kids and adolescents they act as benign tumours while in adults they have the tendency to be malignant.<sup>[20]</sup> Histologically, they are presented with neurogenic elements more often than mesodermal component, some tumours may be arising from the liver, intestinal, esophageal components (endodermal). Their grading is based on segments of primitive neuroepithelium. Providing they can be fully surgically removed they have a good prognosis.<sup>[18,21]</sup>

The case presented here is the first report of a combination of immature embryonic teratoma in the submandibular region with a predominantly primitive neuroepithelium in Edwards syndrome.

Of interest is also the ureteral anomaly represented by a double kidney and an ectopic ureter of the other kidney.

## CONCLUSIONS

Live births with Edwards syndrome are rare due to spontaneous termination of early pregnancy and good prenatal diagnosis with both ultrasound and screening tests. Patho-

logical diagnosis in these children supports the clinical one, which allows to detect malformations as well as to support the subsequent genetic research of paraffin blocks. Besides the characteristic malformations for trisomy 18 in our case we discovered an immature teratoma in the submandibular region. To date, we have not found another described case of this tumour with such localization in a child with Edwards syndrome.

## Author contributions

G.E.: autopsy case of Dr. Gerakova, macroscopic photos taken, wrote the draft of the article and translated the text. S.G.: final design and writing of the article, literature review, wrote the abstract, microscopic photos.

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# Отчёт о редком случае синдрома Эдвардса с незрелой тератомой в поднижнечелюстной области и обзор литературы

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## Резюме

Трисомия 18 (синдром Эдвардса) была впервые описана Эдвардсом и др. в 1960 году. Заболевание является вторым наиболее распространённым синдромом аутосомной трисомии у мужчин. Распространённость среди младенцев оценивается как 1/6000-1/8000. Пострадавшие имеют высокий уровень смертности – только 4% могут выжить в первый год.

Исследование иллюстрирует первый зарегистрированный случай синдрома Эдвардса с незрелой тератомой в подчелюстной области.

33-летняя повторнобеременная женщина имела нормальное антенатальное течение до 36 недели беременности. Через два часа после родов ребёнок был доставлен в отделение для новорожденных, где было описано несколько пороков развития: опухолевидное образование размером с грецкий орех в правой поднижнечелюстной области, аномалия уха, микрогнатия с высоким сводчатым нёбом, перекрытием пальцев и деформацией стоп. Проведен генетический тест, подтвердивший трисомию 18. Через 26 дней искусственной вентиляции лёгких и оксигенотерапии у новорожденного развилась гиалиново-мембранная болезнь, дилатация лёгочной артерии и правых отделов сердца, тромбоз правого предсердия и эти состояния были определены как причина смерти.

Вскрытие и гистологическое исследование подтвердили вышеупомянутые пороки развития, обнаружив также почку с удвоенной чашечно-лоханочной системой справа и эктопированный мочеточник в левой почке. Поднижнечелюстная опухоль была определена как незрелая тератома.

**Заключение:** Это первый случай в литературе новорожденного с синдромом Эдвардса в сочетании с незрелой тератомой.

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## Ключевые слова

синдром Эдвардса, незрелая тератома, трисомия 18, поднижнечелюстная область

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