

# Anatomy and ontogeny of renoureteral malformations in children

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**Abstract.** Introduction: Renal malformations may be part of chromosomal or sporadic syndromes (non-syndromic). This is an important cause of perinatal mortality and morbidity. Material and method: This is a retrospective study conducted on a total of 3 cases of dead fetuses and newborns autopsied in the Anatomical Pathology Laboratory of Cluj County Emergency Hospital. Both macroscopic and microscopic studies of the kidney have been conducted in all renal malformations detected. Results: Diagnosed renal malformations have been related to plurimalformative syndromes in three cases: one case of Charge syndrome, one case of Meckel-Gruber syndrome and one suspected case of Kallmann syndrome. Conclusions: Given the increased risk of recurrence of renal anomalies and of syndromes associated with renal anomalies, as well as the high incidence of undiagnosed syndromes after standard antenatal and perinatal examination, attention must be drawn on the importance of neonatal autopsy in order to provide further genetic counseling.

**Key Words:** renoureteral malformations, plurimalformative syndrome, ontogeny

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## Introduction

Renal malformations may be part of chromosomal or sporadic syndromes (non-syndromic). Understanding the significant events of embryonic kidney development is essential for the diagnosis of renal anomalies and for the interpretation of the relationships between various congenital anomalies found in one single patient.

Embryonic kidney development is a complex process involving sequential interactions between epithelial and mesenchymal cells, governed by certain gene expression products. This interaction determines cell proliferation, apoptosis and cell differentiation (Moore *et al* 2006; Lermann *et al* 2007).

Renal anomalies are an important cause of perinatal mortality and morbidity. Although ultrasound examination is very important in assessing the prenatal diagnosis of congenital renal anomalies, in medical abortion or perinatal death, fetal autopsy and histopathology of the kidneys have an overwhelming contribution to confirm the clinical diagnosis. It's important to establish the differential diagnosis between autosomal recessive polycystic kidney disease (ARPKD), where there is a 25% risk of recurrence in subsequent pregnancies, and renal cystic dysplasia, with a 3% risk of recurrence (Chenet *et al* 2005; Kumari *et al* 2008).

Studies have displayed a significant number of kidney anomalies that are not detected during prenatal screening (42.8%) or for which postmortem examination provides additional information important for further genetic counseling (Giordano *et al* 2011).

## Material and method

This is a retrospective study conducted on a total of 3 cases of dead fetuses autopsied in the Anatomical Pathology Laboratory of Cluj County Emergency Hospital. Both macroscopic and microscopic studies of the kidney have been conducted in all renal malformations detected. Microscopic study has been carried out using the classical hematoxylin and eosin (H&E) staining procedure (2X, 4X, 10X, 20X).

## Results

### Case 1 - CHARGE syndrome

The first case studied is that of a female fetus suspected of having CHARGE syndrome, dead in utero at the gestational age of 28 weeks.

Macroscopic examination of the kidney revealed a fetal lobed kidney, bilateral hydronephrosis, an increased volume of the right kidney (6/3/2.5 cm in diameter), bilateral ureteral stenosis in the

lower third, left kidney with the same cross-section aspect, bilateral adrenal hypoplasia. According to Cohen *et al* the normal size of the kidney at that age is of 3.4 cm (Cohen *et al* 1991). Microscopic examination of the kidney revealed nephroblastomatosis, six glomerular generations, interstitial blood stasis and hematic infiltrates, calyceal dilatation. Autolytic changes in the adrenal gland have also been observed.

This case presented an association of parameters in the cheilognathopalatoschisis cephalic extremity, such as the flattened implantation base of the nose, a 1.5 cm interocular distance, a 1.5 cm length of the palpebral fissure. The brain presented subarachnoid hemorrhage with both convexity and interhemispheric fissure, interhemispheric fissure in the posterior and middle third, absent in the anterior third, bilateral aplasia of the olfactory bulb, agenesis of the cerebellar vermis with dilatation of the fourth ventricle.

Polydactyly occurred in the right upper limb, an extra 5/2 mm finger joined by a 2 mm pedicle with finger number 5.

Examination of the cardiovascular system revealed cardiomegaly, dilatation of the right atrium, hypoplastic left ventricle, atrial septal defect, subvalvular ventricular septal defect (1 mm in diameter), dysplastic pulmonary valve, aorta emerging from the right ventricle, patent ductus arteriosus. The emerging pulmonary artery was observed at 1.5 cm below the aortic valve.

The digestive tract of the fetus presented subhepatic cecum and appendix, a double “loop” of the descending portion of the colon, hypoplastic gallbladder surrounded by liver parenchyma. Examination of the respiratory tract revealed right lung with incomplete lobation and left lung with additional fissures of the upper lobe.

### Case 2 –Meckel Gruber syndrome

Meckel Gruber syndrome was diagnosed in a female abortion at the gestational age of 19 weeks.

Autopsied cadaver showed a 4.5/2.5/2 cm kidney with the presence of numerous cysts in both the cortex and the medulla (1-5 mm in diameter).

Microscopic examination of the kidney revealed renal parenchyma with numerous cysts covered with simple flat or cylindrical epithelium, loose swollen stroma with focal hematic suffusions (Fig. 1).

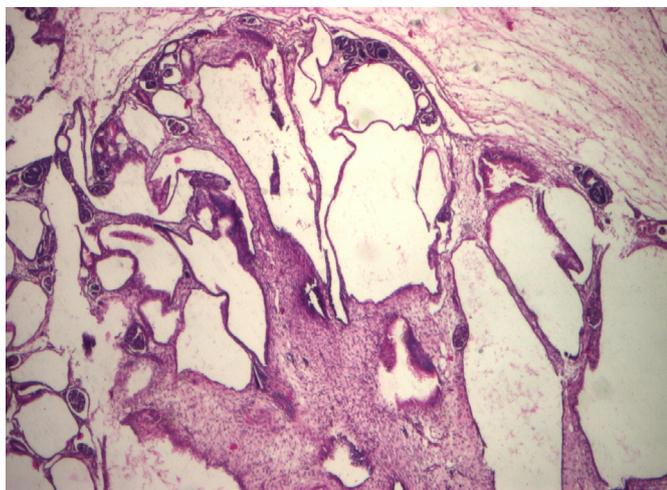


Figure 1. HE 2x rudimentary glomeruli, cystic structures

Examination of the cephalic extremity revealed palatoschisis, lowset ears, flattened nose base, 3/2 cm posterior fontanelle. The musculoskeletal system presented associated polydactyly (6 fingers) in upper and lower limbs and thumbs in lower limbs (Fig. 2).



Figure 2. Polydactyly

Occipital encephalocele was found in the nervous system.

The digestive system revealed the presence of subhepatic appendix.

### Case 3 – suspicion of Kallmann syndrome

The next case was that of a plurimalformed male fetus aged 33 weeks. Macroscopic examination of the urogenital tract revealed the following: 7.5/5.5/5 cm cystic right kidney, without evidence of ureter presence, 5/3.5/2.5 cm left kidney, left ureter, the emergence of the basin created a ‘loop’ with inward concavity and multiple codes, associated agenesis of the right adrenal gland and hypoplasia of the left adrenal gland (Fig. 3).

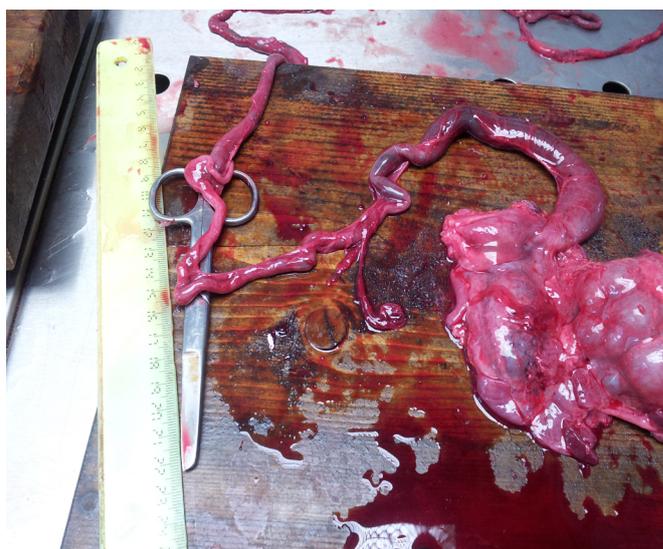


Figure 3. Left-sided hydronephrosis. Left-sided ureteral stenosis

Microscopic examination of the kidneys revealed the following: left kidney with 13 glomerular generations, glomerular stasis and hematic cortical infiltration, immature cartilage islands, right kidney with numerous cystic structures and normal-looking

glomeruli, isolated tubular structures with immature mesenchyme. The histological aspect described belongs to that of a multicystic dysplastic kidney (Fig. 4).

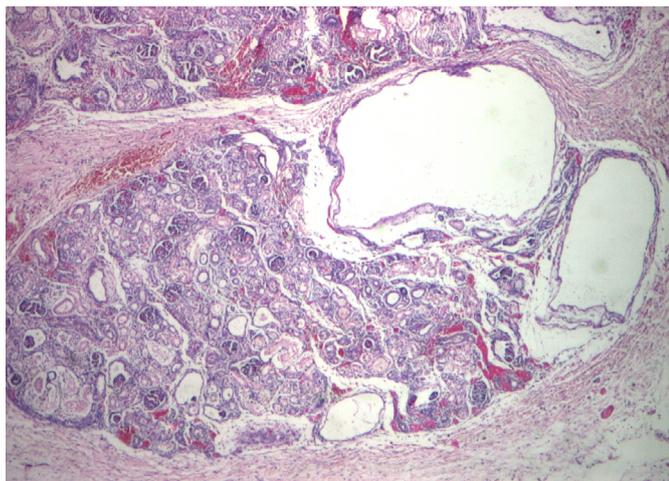


Figure 4. HE 2x cystic structures, mesenchyme, and rare glomeruli

Examination of the reproductive system showed intra-abdominal testes.

Examination of the cephalic extremity showed: lowset ears, short neck, small-sized viscerocranium, narrow forehead, 2 cm interocular distance, 1.7 cm length of palpebral fissure, broad nasal root, bilateral choanal atresia, sagittal view, micrognathia. Examination of the brain showed the following: bloody swelling, subperiosteal hemorrhage, 4.5/4.7 cm anterior fontanelle, 2.5/1.5 cm posterior fontanelle, subarachnoid hemorrhage, holoprosencephaly, absence of olfactory tracts and bulbs.

The digestive system noted the presence of omphalocele and anal atresia.

Cardiovascular examination revealed citrine serous pericardial fluid, pericardial petechiae, ventricular septal defect (membranous), pulmonary valve stenosis and pulmonary valve dysplasia (0.4 cm), with one cusp, patent foramen ovale, patent ductus arteriosus (Fig. 5).

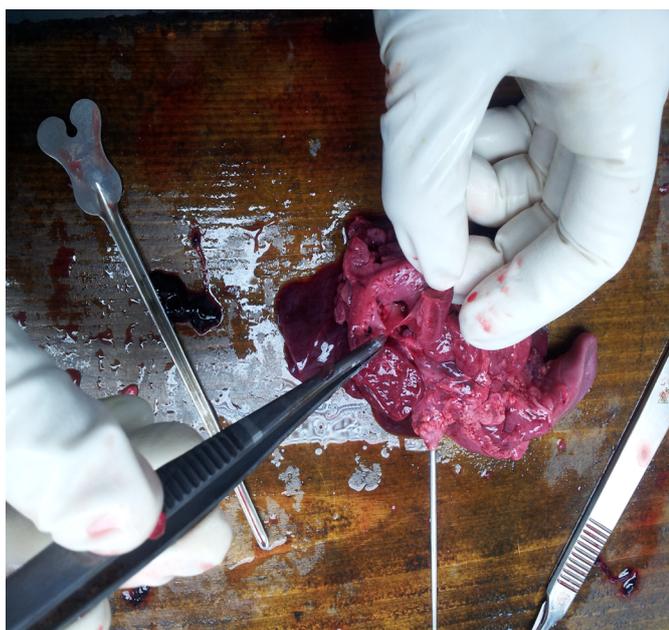


Figure 5. Ventricular septal defect

The presence of 5.5/2.5/1 cm and 3/1.1/0.4 cm supernumerary spleen was also observed.

Examination of the respiratory tract showed the presence of 10 ml hemorrhagic serous pleural fluid in the right pleural cavity, purple-colour lungs.

Placenta was 19.5/17/1 cm in size, with a 5/3 cm retroplacental hematoma, umbilical cord inserted 4 cm into the nearest edge of the placental disc, with a length of 13 cm and extremely swollen.

## Discussions

Renal anomalies are an important cause of perinatal mortality and morbidity. Renal congenital anomalies in fetuses and newborns are frequently associated with head abnormalities (somatic component) and incomplete pulmonary lobation.

Meckel-Gruber syndrome is an autosomal recessive disorder characterized by a large variety of systemic malformations, of which the most common are multicystic dysplastic kidney, polydactyly, occipital encephalocele, cystic changes and liver fibrosis. Meckel-Gruber syndrome is diagnosed with equal incidence in male and female infants. Once a couple conceived a child diagnosed with Meckel-Gruber syndrome, there is a 25% chance of recurrence of the syndrome in subsequent pregnancies. Meckel-Gruber syndrome can be confirmed by the detection of mutations in the MKS1, MKS2 and MKS3 genes. Comparison of clinical data demonstrates a low frequency of polydactyly in patients with mutations in the MKS3 gene (Alexiev *et al* 2006). Neonatal autopsy is crucial for diagnosis of associated anomalies (Panduranga *et al* 2012; Eckmann-Scholz 2012).

The most common renal anomalies observed in patients diagnosed with Meckel-Gruber syndrome are bilateral renal cystic dysplasia, renal hypoplasia, renal agenesis, “horseshoe” kidney and duplicated ureter. Other congenital abnormalities that can be identified in patients with Meckel-Gruber syndrome are that of the nervous system (Dandy-Walker malformation, microcephaly, holoprosencephaly, anencephaly, cerebellar hypoplasia), anomalies of the cephalic extremity (micrognathia, microphthalmia, cheilognathopalatoschisis) and cardiac anomalies. (Alexiev *et al* 2006) In this study, female fetus aged 19 weeks and diagnosed with Meckel-Gruber syndrome also presented digestive malformations aside from the malformations described in the literature (subhepatic appendix). Differential diagnosis of patients with Meckel-Gruber syndrome is achieved with the help of Smith-Lemli-Opiz syndrome, trisomy 13, Bardet-Biedl syndrome and Joubert syndrome. Autopsy provides useful information in differential diagnosis and can be used to assess the risk of recurrence in subsequent pregnancies.

Initial diagnostic criteria for CHARGE syndrome required the presence of four out of the six characteristics: coloboma, heart defects, choanal atresia, retarded growth and development, genital hypoplasia, cranial nerve anomalies and ear anomalies/deafness. For the moment, the presence of major and minor diagnosis criteria is considered. Major criteria includes those characteristics that commonly occur in CHARGE syndrome but are rare in other diseases. Minor criteria not necessarily occur rarely, but are less specific to CHARGE syndrome (Blake *et al* 2006; Writzl *et al* 2007).

The diagnosis of CHARGE syndrome should be suspected in any infant presenting all four major characteristics: choanal atresia, coloboma, ear and cranial nerve abnormalities. Also, patients

with three major characteristics and three minor characteristics have a high probability to display CHARGE syndrome. In some cases, Charge syndrome is difficult to detect in the neonatal period and it is suspected in any child who presents one or two major criteria, and some minor criteria. Charge syndrome may also be suspected in the absence of coloboma or choanal atresia. Each feature can vary in different children from being absent to being severe (Blake *et al* 2006; Writzl *et al* 2007).

In this study, renoureteral malformations detected in patients diagnosed with CHARGE syndrome have been: bilateral hydronephrosis, bilateral ureteral stenosis and persistent fetal lobulation. Other abnormalities identified in patients diagnosed with CHARGE syndrome were: hypoplasia of the adrenal gland, cheilognathopalatoschisis, flattened implantation base of the nose, arhinencephaly, vermian agenesis, polydactyly, atrial septal defect, ventricular septal defect, right ventricle with dual ejection path, incomplete pulmonary lobation of the right lung and additional fissures in the left lung. The case of CHARGE syndrome diagnosed in this study also presented digestive abnormalities that are rarely mentioned in the literature, namely hypoplastic gallbladder, subhepatic location of the appendix and of the cecum. Most cases of CHARGE syndrome are sporadic, the presence of isolated elements of the syndrome should determine the prompt and detailed assessment of family members in order to achieve further genetic counseling. Children with CHARGE syndrome require intensive medical treatment and numerous surgeries. Genetic diagnostic methods (karyotype to confirm the integrity of chromosomes 22, 14 and 9, and the CHD7 gene mutation in CHARGE syndrome test, mutations in the MKS gene in Meckel-Gruber syndrome) are of critical importance in the diagnosis.

Kallmann syndrome is characterized by the presence of hypogonadotropic hypogonadism associated with anosmia/hyposmia secondary to aplasia or hypoplasia of the olfactory bulbs and tracts. Anomalies of the kidney are more common in patients diagnosed with Kallmann syndrome than it was previously believed, the most frequent being: unilateral or bilateral renal agenesis, renal hypoplasia, renal malrotation, "horseshoe" kidney, hydronephrosis, vesicoureteral reflux and duplicated ureter. Mutations of the KAL gene, which is actively expressed in the mesonephros and metanephros during embryogenesis, cause renal malformations (Zenteno *et al* 2009). In this study, renoureteral malformations identified in patients diagnosed with Kallmann syndrome were: right multicystic dysplastic kidney, left hydronephrosis, left renal hypoplasia and ureteral stenosis. There were other associated disorders, such as: agenesis of the olfactory tracts and bulbs, testicular ectopy, malformations of the external genitalia, abnormalities of the cardiovascular and digestive systems.

Clinical diagnosis was correlated with anatomopathological diagnosis in abortions diagnosed with CHARGE syndrome. Diagnosis in the two cases of Meckel-Gruber syndrome and Kallmann syndrome was established after the anatomopathological examination. Absence of concordance or partial concordance between clinical diagnosis and anatomopathological data highlights the importance of neonatal autopsy in order to assess the diagnosis of plurimalformative syndromes.

## Conclusion

The increased risk of recurrence of kidney malformations and of syndromes with associated renal anomaly components, as well as the high incidence of undiagnosed syndromes after standard antenatal and perinatal examination must draw attention to the importance of neonatal autopsy in providing further genetic counseling.

Renoureteral malformations in fetuses and newborns are frequently associated with head abnormalities (somatic component) and incomplete pulmonary lobation.

Multicystic dysplastic kidney and obstructive hydronephrosis have both revealed an increased volume of the kidneys compared to the normal kidney size corresponding to the gestational age. Neonatal autopsy is decisive for the diagnosis of plurimalformative syndromes.

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