



# Multicystic dysplastic kidney: a new association of Wolcott–Rallison syndrome

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## Summary

Wolcott–Rallison syndrome (WRS) is a rare autosomal recessive disorder due to mutations in the *EIF2AK3* gene. It is characterized by permanent neonatal diabetes mellitus, skeletal dysplasia, liver impairment, neutropenia and renal dysfunction. Liver is the most commonly affected organ and liver failure is the commonest cause of death in this syndrome. The *EIF2AK3* gene encodes a transmembrane protein PERK, which is important for the cellular response to endoplasmic reticulum (ER) stress. The absence of PERK activity reduces the ER's abilities to deal with stress, leading to cell death by apoptosis. On acquiring febrile illness, affected patients suffer from liver injury, which may progress into liver failure and death. Renal involvement is less common and is mainly in the form of functional renal impairment at the advanced stage of the disease. Structural renal anomalies have not been reported in WRS. We report a 6-month-old girl who presented with neonatal diabetes on day 1 of life. Her genetic testing confirmed WRS due to missense mutation in the *EIF2AK3* gene (c.2867G>A, p.Gly956Glu). Parents are first-degree cousins and both are heterozygous carriers to the mutation. 2 paternal uncles had the same mutation and died of liver disease at 1 and 14 years of age. Neither had a renal disease. She presented with hematuria during a febrile illness at the age of 5 months. Ultrasound scan showed right ectopic multicystic dysplastic kidney (MCDK). To the best of our knowledge, this is the first patient with WRS who is reported to have an MCDK disease.

## Learning points:

- Neonatal diabetes should be considered in babies presenting with early hyperglycemia particularly if there is a family history.
- Genetic diagnosis in neonatal diabetes enables disease confirmation, genetic counseling and anticipation of potential complications during concomitant situations such as acute illness, trauma or major surgery.
- There is lack of phenotype–genotype correlation in Wolcott–Rallison syndrome.
- Structural kidney abnormality, in our case MCDK, can be seen in WRS.

## Background

Wolcott–Rallison syndrome (WRS) is a rare autosomal recessive multisystemic disorder due to biallelic mutations in *EIF2AK3* gene. The syndrome is characterized by permanent neonatal diabetes mellitus, skeletal dysplasia and recurrent liver disease triggered by viral illnesses and stress (1). Other features of the syndrome include renal

dysfunction, failure to thrive, neutropenia, exocrine pancreatic insufficiency, hypothyroidism, recurrent infection and developmental delay.

In 2000, mutations in the *EIF2AK3* gene were identified in few patients with WRS (1). Since then, almost all patients with classical WRS features have *EIF2AK3*



mutations. The *EIF2AK3* gene encodes a transmembrane protein called protein kinase R-like endoplasmic reticulum kinase (PERK), which is important for the cellular response to endoplasmic reticulum (ER) stress. The absence of PERK activity reduces the ER's abilities to deal with stress, leading to cell death by apoptosis in many tissues (2).

Liver pathology is the most frequent and the leading cause of death in WRS patients. In a cohort of 28 patients with WRS, 87% had an associated liver disease while 21% had renal impairment (3). In this cohort, none of the patients had a structural kidney anomaly but some had functional renal impairment. Renal involvement in the syndrome is typically in the form of renal failure at a later stage of the disease deterioration with initial renal function being normal. In this study, all patients who had renal impairment had so during the period of febrile illnesses and liver impairment (3).

We report a case of WRS who presented with hematuria due to MCDK disease. To the best of our knowledge, this is the first case of WRS to be reported to have a structural kidney anomaly.

## Case presentation

We report a 6-month-old female who was born preterm at 30 weeks and 6 days of gestation. She was small for gestational age (birth weight 1.1 kg). She presented with hyperglycemia on the first day of life and was started on insulin on day 2. Initial insulin treatment was in the form of insulin infusion at 0.05 unit/kg/day. She was shifted to subcutaneous insulin after 2 days when she required 1 unit/kg/day of a single dose of NPH insulin. The baby remained well and gained weight but her

glucose remained high. Her pre-and post-feed glucose range were 9.4–11.4 and 14–16 mmol respectively. Insulin requirement increased to 2 units/kg/day and was shifted to basal bolus regime (insulin Detemir and insulin Aspart) at the age of 7 days. At the current age of 6 months, she remained on insulin at a dose of 2 unit/kg/day.

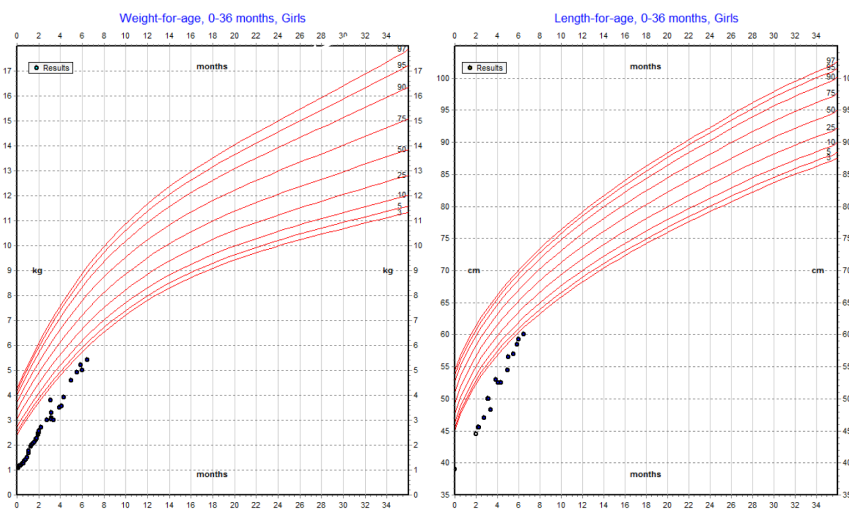
Parents are first-degree cousins and of Irani origin. The baby had 5 siblings who are all healthy. She had 2 paternal uncles who had neonatal diabetes. Both had a genetic diagnosis of WRS and died of liver failure at 1 and 14 years.

## Investigation

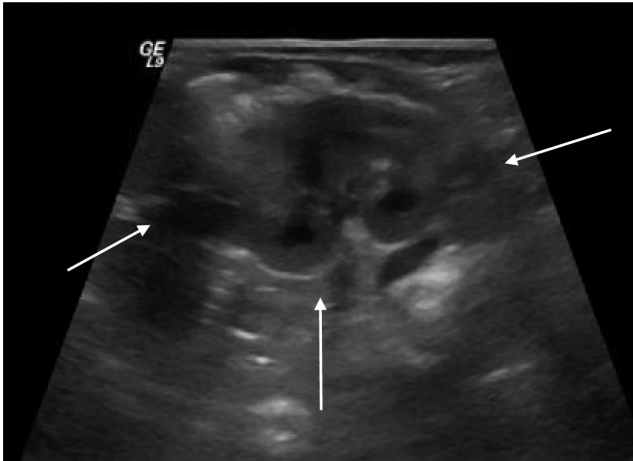
Investigations showed low c peptide of 0.41 nmol/L (NR: 0.37–1.47), normal liver and kidney function tests initially. Negative ILA2, GAD and insulin antibodies. In view of the early presentation with diabetes and the positive family history of neonatal diabetes, she had a genetic test for WRS. Coding and flanking intronic regions of the *EIF2AK3* (AF110146.1) gene were analyzed by Sanger sequencing. The test revealed that she is homozygous for *EIF2AK3* missense mutation (c.2867G>A, p.Gly956Glu). Both parents were confirmed to be heterozygous carriers of the gene mutation. Both her deceased parental uncles were homozygous with the same mutation.

## Outcome and follow-up

She grew well on the centile charts for length and weight (Fig. 1) and her glucose profile was well controlled on insulin. At the age of 3 months, she had fever and upper respiratory tract infection and presented with macroscopic



**Figure 1**  
Growth chart showing progress in weight and height.



**Figure 2**  
Ultrasound scan showing right ectopic MCDK. Arrows highlight the kidney outlines.

hematuria. Urine was red-brown macroscopically. Urine microscopy showed 250 cell/ $\mu$ L red blood cells. Urine was negative to nitrite, protein and ketones. Urinary urobilinogen and bilirubin were negative. Urine culture showed no growth. USS showed right kidney is low-lying (ectopic) and not visualized in the right renal area. It measured 2.3 cm in length with a cortical thickness of 0.1 cm compared to the left, which measured 5.12 cm in length and has a cortical thickness of 0.5 cm (Fig. 2). Right kidney has multiple cysts with the largest measuring 0.7  $\times$  0.74 cm (Fig. 3). The right ureter is atretic. The features are classical of ectopic MCDK.

During the febrile illness, kidney function tests remained normal, liver transaminases were high with ALT of 462 IU/L (NR: <31) and AST of 129 IU/L (NR: <32). Total bilirubin was 95  $\mu$ mol/L (NR: <17). Her neutrophil count was low at  $1.6 \times 10^9$ /L and coagulation screen was normal.

## Treatment

She received conservative treatment for the viral upper respiratory tract infection. Her insulin was adjusted as per the sick days rules management. The hematuria subsided and her liver transaminases normalized within 5 days. Her insulin regime remained as basal bolus with and returned to an average dose requirement of 2 units/kg/day.

## Discussion

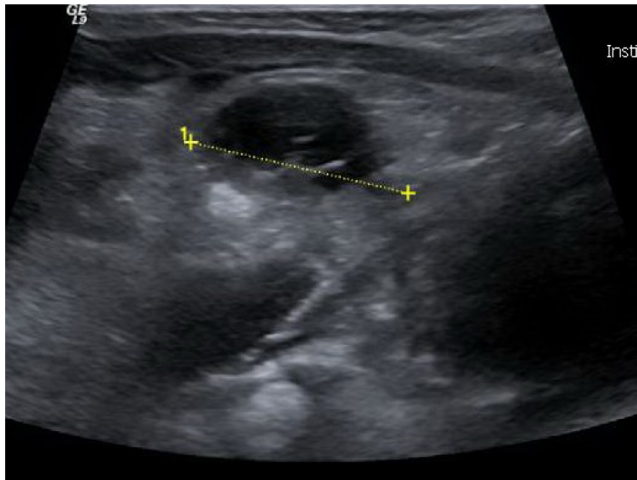
MCDK is the most common congenital cystic anomaly of the kidney. It is characterized by multiple non-communicating cysts within the kidney. Unlike other

cystic kidney diseases, such as the dominant and recessive forms of polycystic kidney where there is a clear inherited pattern, MCDK occurs sporadically and can remain clinically undetected and asymptomatic (4). MCDK is a known associating feature of maturity-onset diabetes of the young type V (MODY5) caused by mutations in the hepatocyte nuclear factor 1-beta (5). However, it has not been described with neonatal diabetes and has not been reported in WRS. The presence of MCD in our patient in the background of WRS could either be a new association or it could be explained by the increased frequency of autosomal diseases in patients born in a consanguineous family. Woods and coworkers found that the amount of homozygosity is 11% in patients with autosomal recessive disease whose parents are first cousins (6). Investigating the siblings for cystic kidneys or testing for cystic kidney disease in a gene panel could shed some light on the etiology of the disease in the index case.

The renal involvement in WRS is well known (3). However, the association of MCDK might be debatable in view of the fact that the absence of PERK activity triggering apoptosis is mainly seen in secretory cells like the hepatocytes and the pancreatic cells rather than renal tubular epithelial cells. In the meantime, there are findings on WRS non-diabetes related-renal pathology that are in favor of this association. Immunohistochemistry on these biopsies showed abnormal mitochondria and other features that are linked to ER (7).

MCDK is mostly asymptomatic; however, it presented with hematuria in this baby. We attribute the presentation to the cell death induced by the ER reaction during the stress of the febrile illness she had. This reaction is known to be the mechanism leading to hepatic failure in most WRS patients.

Targeted disruption of the *EIF2AK3* gene in mice also causes diabetes because of the accumulation of unfolded proteins triggering B-cell apoptosis. Although no renal abnormality has been described in *EIF2AK3* knockout mouse models, Brickwood *et al.* showed striking *EIF2AK3* expression during human fetal renal development. Authors described robust expression in the renal capsule and inner stromal tissue that surrounds *EIF2AK3* and the developing tubules (8). The strong gene expression in the targeted tissues prompted the concept of utilizing elective liver, pancreas and kidney transplant to manage complication of the syndrome. We have previously reported a successful liver transplant in WRS child (9). This child presented with fulminant liver failure and liver function remained normal 8 years post transplant despite repeated febrile illnesses. This child had a wide spectrum



**Figure 3**  
Ultrasound scan showing large cyst in the right MCDK. The arrow points to the cyst and the dotted line shows the largest dimensions.

of WRS-associated morbidities including skeletal dysplasia and cytopenias. However, he has no renal involvement.

The *EIF2AK3* missense mutation located at Exon 14, p.Gly956Glu (c.2867G>A) detected in our patient was previously reported and is known to be pathogenic/causative of WRS (10). The 2 uncles who had WRS due to the same mutation died at 1 and 14 years of age. In both, liver disease was the leading cause of death. Although both had diabetes, liver disease, anemia and skeletal dysplasia, neither had renal disease except at a later stage of the disease when renal failure was a part of multiorgan failure. We have reported lack in phenotype–genotype correlation in a large cohort of WRS. In this cohort, lack of correlation was both intra- and interfamilial (4). Variation in the onset, nature and severity of a WRS comorbidities is seen in many cohorts of WRS (10). This variation can be attributed to several factors including variable *EIF2AK3* gene expression, epigenetic factors and presence of other modified genes.

## Conclusion

MCDK disease can be seen in WRS. We postulate that the mechanism causing hematuria is related to failure of the ER stress mechanism due to the absence of the PERK enzyme of the mutant gene. This is a similar mechanism leading to the commonly seen liver impairment in this syndrome.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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### Patient consent

Written informed consent has been obtained from the mother of the patient.

### Author contribution statement

Dr F Al-Zidgali diagnosed diabetes in the patient, obtained the family history and recognized the features suggestive of neonatal diabetes. Dr B Ofoegbu managed the baby during her stay in the special care baby unit, wrote the initial report and referred her to endocrinology department. Dr A Deeb managed the baby's diabetes, advised to perform the genetic testing, wrote and submitted the manuscript. All authors revised and approved the submitted version of the manuscript.

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