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SECTION: CASE REPORT

Two non-familial cases of Galloway-Mowat syndrome carrying the homozygous mutations of WDR73 and TP53RK

Dois casos não familiares de síndrome de Galloway-Mowat portadores das mutações homozigóticas de WDR73 e TP53RK

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Abstract: Galloway–Mowat syndrome (GAMOS) is a rare hereditary disease manifested as a combination of nephrotic syndrome and central nervous system impairment. To date, many GAMOS cases attributed to various gene mutations have been reported such as *WHAMM, NUP107, WDR73, OSGEP*, and *TP53RK*. We detected two novel homozygous mutations of *WDR73* "NM_032856:c.G287A:p.R96K" and *TP53RK* "NM_033550:c.A193O:p.K65Q" in two female kids of the consanguineous parents from different families using whole exome sequencing. Both patients almost manifested similar neurodegenerative phenotypes, including developmental delay, microcephaly, hypotonia, and brain atrophy on magnetic resonance imaging during infancy. *WDR73*-positive GAMOS case manifested a late-onset minimal nephrotic syndrome at the age 4 years while *TP53RK*-positive case presented nephrotic syndrome at the age 1 which progressed to steroid-resistant nephrotic syndrome due to lack of remission after 4-6 weeks of initial treatment with prednisone. Despite the brain abnormalities and the onset time difference of renal abnormalities, both patients are still alive. Given the heterogeneity of the renal phenotype among GAMOS types, accurate recognition of expanding spectrum of phenotype findings and regular renal function screening are necessary for an early diagnosis and timely treatment.

Keywords: Galloway–Mowat syndrome, mutation, genetic syndrome.

Resumo: A síndrome de Galloway-Mowat (GAMOS) é uma doença hereditária rara que se manifesta como uma combinação de síndrome nefrótica e comprometimento do sistema nervoso central. Até o momento, foram relatados muitos casos de GAMOS atribuídos a várias mutações genéticas, como WHAMM, NUP107, WDR73, OSGEP e TP53RK. Detectamos duas novas mutações homozigóticas de WDR73 "NM_032856:c.G287A:p.R96K" e TP53RK "NM_033550:c.A193O:p.K65Q" em duas crianças do sexo feminino, de pais consanguíneos de diferentes famílias usando o exoma completo de sequenciamento. Ambos os pacientes manifestaram fenótipos neurodegenerativos semelhantes, incluindo atraso no desenvolvimento, microcefalia, hipotonia e atrofia cerebral por ressonância magnética durante a infância. O caso GAMOS positivo para WDR73 manifestou síndrome nefrótica mínima de início tardio aos quatro anos de idade, enquanto o caso positivo para TP53RK apresentou síndrome nefrótica com um ano de idade, que progrediu para síndrome nefrótica resistente a esteroides devido à falta de remissão após quatro a seis semanas de tratamento inicial com prednisona. Apesar das anormalidades cerebrais e da diferença de tempo de início das anormalidades renais, ambos os pacientes ainda estão vivos. Dada a heterogeneidade do fenótipo renal entre os tipos de GAMOS, o reconhecimento preciso do espectro em expansão dos achados fenótipos e a triagem regular da função renal são necessários para um diagnóstico precoce e tratamento oportuno.

Palavras-chave: síndrome de Galloway-Mowat, mutação, síndrome genética.

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Introduction

Galloway–Mowat syndrome (GAMOS) is a rare hereditary disease manifested as a renal–neurological impairment, steroid-resistant nephrotic syndrome (SRNS), microcephaly, and developmental delay (1). To date, many GAMOS cases attributed to various gene mutations such as *WHAMM, NUP107, WDR73, OSGEP,* and *TP53RK* have been reported (2–6). Truncating variant in *WHAMM* was found in Amish population in addition to bi-allelic *WDR73* mutation. *WDR73* and *WHAMM* are located closely, and both are founder mutations. Homozygous WDR73 mutation is primarily responsible for GAMOS, and the clinical phenotype in *WHAMM* mutations is not clear (2) Here, we've presented two girls who referred to the clinic (respectively, at the age 4 and 1) with similar manifestations, including developmental delay, microcephaly, hypotonia, brain atrophy on magnetic resonance imaging (MRI), and nephrotic syndrome. Aim of this report is analyzing the genetic, biochemical, and clinical features of these GAMOS patients in hope of better recognition for its therapeutic management.

Patient Recruitment and Phenotyping

Two patients who had referred to our private clinic (located in Ahvaz city of Iran) with GAMOS--related clinical manifestations were recruited for this study and also registered in Chronic Renal Failure Research Center, Department of Pediatric Nephrology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran for further investigations. The patients' parents provided informed consent for voluntary participation in this study and whole exome sequencing. The study was approved by the ethics committee of Chronic Renal Failure Research Center, Department of Pediatric Nephrology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran with Ethical Code: IR.AJUMS.HGOLESTAN.REC.1401. Clinical and biochemical information was obtained from the patients' medical records.

Genetic Diagnosis and Case presentations

Genomic DNA isolated from whole-blood samples was used for exome sequencing. Genetic diagnosis was performed in Genetic Lab of Ahvaz Jundishapur University of Medical Sciences, and two novel homozygous mutations of *WDR73* and *TP53RK* were detected in two female kids of the consanguineous parents from different families as follows. The final genetic diagnosis was approved by the clinical geneticists.

Case I

The first patient was the only girl child of the consanguineous parents (cousin relationship) with Arab ethnicity. She was born with a birth weight of 3100g, a height of 48cm, Apgar score 7 at 5-minute, and a head circumference of 31cm from a vaginal delivery at the gestational age of 39 weeks. Her mother had a history of two miscarriages (**Figure 1**).

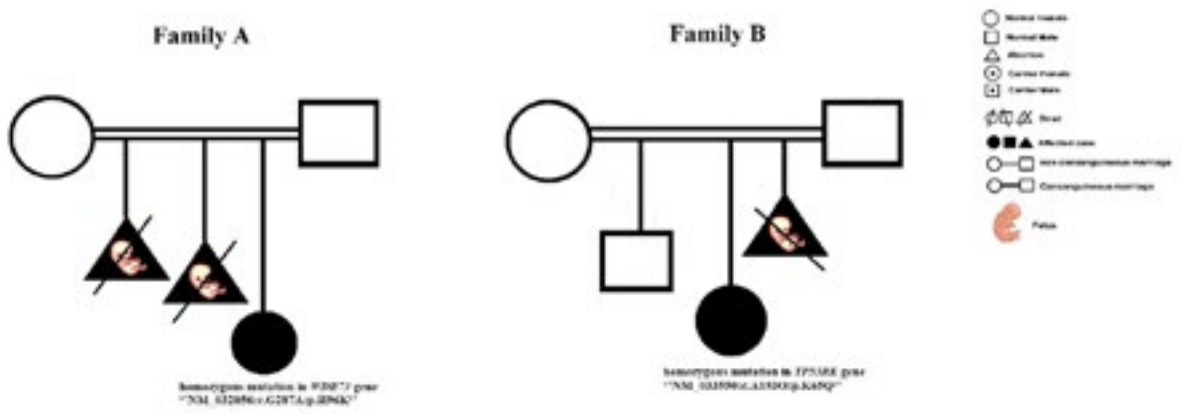

Figure 1. Family Pedigrees of case A and B. filled symbols are indicating the affected status and dashed symbols are deceased children and/or miscarried fetuses (triangle symbols).

Severe developmental delay, microcephaly, hypotonia, and partial optic atrophy were reported in the clinical examinations of infancy. Also, MRI brain atrophy was reported, and edema and proteinuria firstly developed at the age of four years. She represented white matter atrophy with mild subarachnoid space widening as well as cerebellar atrophy (**Figure 2**).

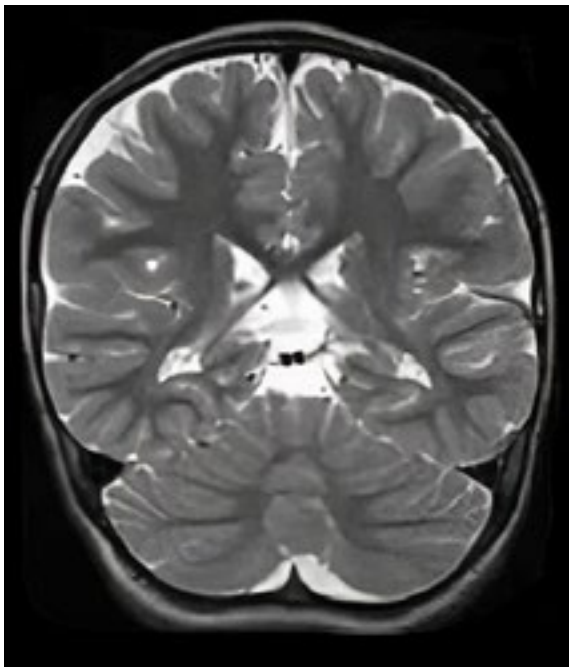

Figure 2. Brain MRI of WDR73-positive GAMOS case. Brain axial T2-weighted MRI of the first patient representing white matter atrophy with mild subarachnoid space widening at age 2 years. MRI, magnetic resonance imaging.

The first case merely had minimal change nephrotic syndrome (MCNS). Under the electron microscopy, MCNS appeared as microvilli growth on the visceral epithelial cells, diffuse loss of podocyte foot processes, and vacuolation. MCNS was treated by prednisone within 8 weeks. Oral dose of 2 mg/kg/day of prednisone was given within the first two weeks and after improvement of proteinuria, it was continued for another 6 weeks at lower doses (1 to 0.25 mg/kg/day).

The first patient had elevated urine protein-to--creatinine (U pr:cr) ratio (21 (945/45)], decreased serum albumin (2.4g/dL), elevated serum cholesterol (339mg/dL), normal serum creatinine (0.4mg/dL), normal C3 (99mg/dL), normal C4 (18mg/dL), and normal antinuclear antibody titer (1:160).

Whole exome sequencing (7) revealed the homozygous mutation in *WDR73* gene "NM_032856:c.G287A:p.R96K" in the first patient.

Case II

The second patient was the second girl child of the consanguineous parents (cousin relationship) with Persian ethnicity (**Figure 1**). She was born with a birth weight of 2800g, a height of 50cm, Apgar score 8 at 5-minute, and a head circumference of 33cm from a vaginal delivery at the gestational age of 38 weeks. Her mother had a history of one miscarriage. In clinical examinations of infancy, developmental delay, microcephaly, hypotonia, and MRI brain atrophy were detected. She had first referred to our clinic with symptoms of edema and proteinuria at the age of 13 months. She had both SRNS and MCNS while the first patient merely had MCNS. Her nephrotic syndrome had progressed to SRNS due to lack of remission after 4-6 weeks of initial treatment with daily prednisone at a dose of 2 mg/kg/day (maximum dose: 60 mg/day). Eventually, SRNS achieved remission after 9 months of treatment with cyclosporine A (starting from 5.0 mg/kg/day up to a maximum dose of 5 mg/kg/day) and tacrolimus (starting from 0.1-0.2 mg/kg/day, twice daily, up to a maximum dose of 5 to 10 µg/L).

The second patient had elevated U pr:cr ratio (18 (450/25)), decreased serum albumin (2.2g/dL), elevated serum cholesterol (332g/dL), normal serum creatinine (0.5mg/dL), normal C3 (111mg/dL), normal C4 (21mg/dL), and normal antinuclear antibody titer (1:170). During clinical examination at the age of 8, weight of 17.5kg, 108cm height, a head circumference of 42cm, mental retardation, and inability to speak were confirmed.

A homozygous mutation in *TP53RK* gene "NM_033550:c.A193O:p.K65Q" was detected in the second patient.

Discussion

Early diagnosis of hereditary disease is very important to its multidisciplinary management. GAMOS is a clinical heterogeneous disorder characterized by a wide range of phenotypic

manifestations (8). Most studies reported that nephrotic syndrome develops in these patients in the first two years of life, and most of them die within the first two years (9). By contrast, our first patient developed nephrotic syndrome at age four and the second patient showed it at age one and she is now eight years old; her brain MRI showed mild subarachnoid space widening and microcephaly and both are still alive. In Braun et al.'s study (9), GAMOS-related kidney involvement caused by mutations in the evolutionarily highly conserved *KEOPS* complex genes developed as a focal-segmental glomerulosclerosis, diffuse mesangial sclerosis, and or other glomerular lesions. Also, podocyte foot process effacement is revealed in electron microscopy (9). In our study, only the second patient revealed SRNS.

If renal impairment occurs before the age of three months, the brain migration abnormalities will be more severe, and the patient usually dies early. But, if kidney involvement occurs later, both kidney disease and developmental brain anomalies will be less severe (10). In this regard, Hyun et al. (11) identified a homozygous *TP53RK* mutation (NM_033550, c.194A > T, p.Lys65Met) in a familial case of GAMOS with three affected siblings. All three patients manifested very early-onset nephrotic syndrome, and subsequent early fatality. Our cases revealed minimal nephrotic syndrome after their first birthday. Despite proteinuria, their other renal biomarkers were normal. Pathologically, renal abnormalities in GAMOS can be like calcineurin inhibitor toxicity with tubular atrophy and striped fibrosis; Other kidney lesions include mesangial proliferation, microcytic dysplasia, minimal change, diffuse mesangial sclerosis, and focal segmental glomerulosclerosis. It seems that there is no age-related renal histological pattern in GAMOS (12). Both of present GAMOS cases almost manifested similar neurodegenerative phenotypes and despite the onset time difference of renal abnormalities, both patients are still alive. This finding is contrary to the claim of previous studies regarding the close relationship between the time and extent of the appearance of the kidney phenotype and the patient's lifespan (13), which demands further research to find the cause of this discrepancy in clinical outcomes.

In previous studies on the patients from Taiwanese ethnic origin, an identical OSGEP gene mutation (c.740G>A transition) has been reported to be associated with SRNS, microcephaly, cerebral pachygyria, and early death before 2 years of age (8, 14). Our first case was a WDR73-positive GAMOS with MCNS and different clinical features from patients with OSGEP-positive GAMOS. Unlike OSGEP-positive GAMOS, patient with WDR73-positive GAMOS mainly presents as an infantile-onset neurodegenerative disease with minor renal involvement, and typical nephrotic syndrome is rarely evident and/or occurs with slow progress in the later years after two years (14, 15). Unlike WDR73-positive case, the TP53RK--positive GAMOS case had referred to the clinic at the age of 13 months with progressed renal function impairment and SRNS. In vivo investigations have recently revealed that TP53RK and OSGEP genes mutations leads to defects in the actin cytoskeleton and reduce the rate of podocyte migration, which are correlated with nephrotic syndrome pathology (14).

Conclusions

We reported two GAMOS cases associated with the novel homozygous mutations of WDR73 ''NM_032856:c.G287A:p.R96K'' and TP53RK ''NM_033550:c.A193O:p.K65Q''. Although both cases almost manifested similar neurodegenerative phenotypes, WDR73-positive GAMOS case manifested a late-onset minimal nephrotic syndrome at the age four years, but TP53RK-positive GAMOS case presented nephrotic syndrome at the age one, which progressed to SRNS. Nevertheless, despite the brain abnormalities and the time difference in the onset of renal function impairment, both patients are still alive. Given the heterogeneity of the renal phenotype among GAMOS types, accurate recognition of expanding spectrum of phenotype findings and regular renal function screening are necessary for an early diagnosis and timely treatment.

Notes

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Conflicts of interest disclosure

The authors declare no competing interests relevant to the content of this study.

Authors' contributions

All the authors declare to have made substantial contributions to the conception, or design, or acquisition, or analysis, or interpretation of data; and drafting the work or revising it critically for important intellectual content; and to approve the version to be published.

Availability of data and responsibility for the results

All the authors declare to have had full access to the available data and they assume full responsibility for the integrity of these results.

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