

## Late-onset nephrotic syndrome with thyroid hypoplasia and nup85 mutation in Galloway-Mowat syndrome: A case report

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### ABSTRACT

Galloway-Mowat syndrome is an autosomal recessive rare hereditary disorder with progressively worsening renal function, neurological and psychomotor abnormalities, microcephaly, facial dysmorphism, and thyroid, adrenal, and ovarian hypoplasia/agenesis. Here, we present the case of a 9-year-old girl who presented with late-onset steroid-resistant nephrotic syndrome with rapid worsening of renal function, microcephaly, hypertelorism, high-arched palate, delayed speech and developmental milestones, poor intellectual function, short stature, hypertension, and hypothyroidism. Magnetic resonance imaging brain was suggestive of cerebral and cerebellar atrophy, hypomyelination, and optic atrophy. Renal biopsy was suggestive of focal segmental glomerulosclerosis. Whole-genome exon sequencing revealed a homozygous mutation in the NUP85 gene. The clinicians should be aware of this rare syndrome and consider it as a possibility in any patient presenting with nephrotic syndrome, microcephaly, and neurological abnormality.

**Key words:** Galloway-Mowat syndrome, Microcephaly, Nephrotic syndrome, NUP85 mutation

Galloway-Mowat syndrome (GMS) is a rare hereditary renal-neurological disease characterized by nephrotic syndrome, microcephaly, and other brain anomalies [1]. Since the first case was reported by Galloway and Mowat in 1968 in two siblings with early-onset nephritic syndrome, microcephaly, and hiatal hernia, more than 60 cases have been reported with varying clinical spectrum [2,3]. It is a clinically as well as genetically heterogeneous disorder and there is no uniform classification for it [4,5]. There are several reports of candidate genes for this disease, WDR73, NUP107, NUP133, WHAMM, and genes encoding four KEOPS (kinase, endopeptidase, and other proteins of small size) subunits, OSGEP, TP53RK, TPRKB, and LAGE3 [6,7].

Here, we report a case of GMS who presented with late-onset nephrotic syndrome, developmental delay, thyroid hypoplasia, and NUP 85 mutation which could be a new variant of this heterogeneous syndrome. This case provides insight into the clinicians about the genetic causes of syndromic children presenting with steroid-resistant nephrotic syndrome and focuses on the importance of genetic testing in such cases.

### CASE REPORT

A 9-year-old girl presented with periorbital swelling, pedal edema, and ascites for 8 weeks. The patient was diagnosed with steroid-resistant nephrotic syndrome at another center. Hypothyroidism was diagnosed at the age of 8 years and she was treated with levothyroxine. The patient was born out of second-degree consanguineous marriage, with an apparently normal elder sibling. The antenatal history was uneventful and birth weight was 3.2 kg. From 6 months of age, the parents noticed delayed developmental milestones, delayed speech, and poor intellectual function.

When admitted to our hospital, her height was 105 cm ( $<-3$  standard deviation [SD]), weight was 21 kg (between  $-2SD$  and  $-3SD$ ), and occipitofrontal circumference was 45 cm (microcephaly). The patient was hypertensive, her blood pressure was 155/110 ( $>95^{\text{th}}$  percentile  $+12$  for her age and height). The patient had hypertelorism, high-arched palate with marked titubation. Abdominal examination showed gross ascites. Neurological examination revealed reduced tone in all four limbs, atrophied muscles, reduced power in bilateral upper and lower limbs, and diminished deep tendon reflexes. Ocular examination was suggestive of optic atrophy.

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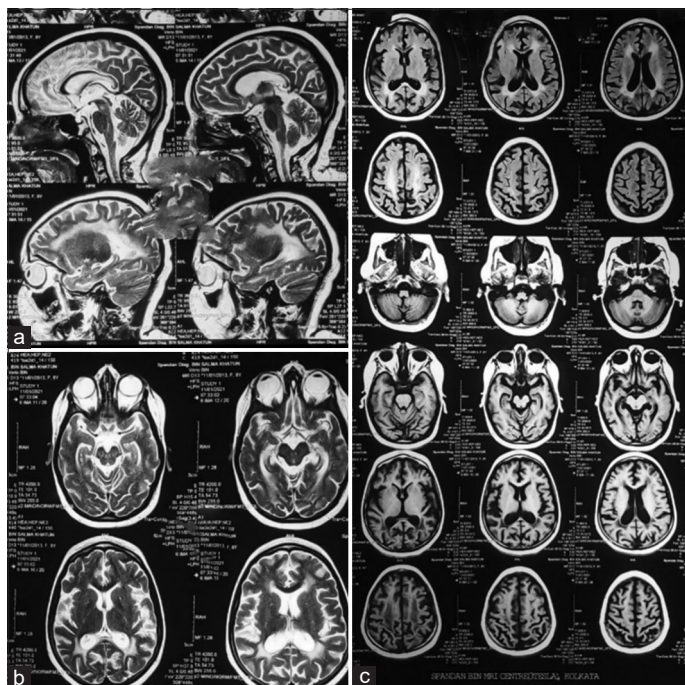
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The baseline investigations showed hemoglobin 12 mg/dl; total leukocyte count 9500 cells/mm<sup>3</sup>; platelet count 2.7 lakh/ $\mu$ l; serum urea 63 mg/dl; serum creatinine 0.79 mg/dl; low serum albumin 0.9 g/dl, low total serum protein 3.2 g/dl; high serum cholesterol 428 mg/dl; and high serum triglyceride 361 mg/dl. Serum thyroid-stimulating hormone was undetectable, luteinizing hormone and follicle-stimulating hormone were low. Urine routine microscopy revealed albumin 3+, red blood cells 1+, and pus cells 1–2. The urine culture was sterile. Twenty-four hours urine protein was 3.7 g/24 h. Hepatitis B, C, and human immunodeficiency virus were negative. Serum complement level (C3 and C4), antineutrophil cytoplasmic antibodies, and antinuclear antibodies profile were normal.

Ultrasonography (USG) abdomen showed normal sized kidneys, raised cortical echogenicity but maintained corticomedullary differentiation. Echocardiography revealed no congenital anomaly and good biventricular function. USG neck revealed hypoplastic thyroid mass (6 mm  $\times$  3 mm) bilaterally. Magnetic resonance imaging brain showed diffuse cerebral atrophy, thinning of the corpus callosum, bilateral optic atrophy, mild cerebellar atrophy, and white matter hypomyelination with empty sella (Fig. 1). However, her electroencephalogram (EEG) was normal.

Kidney biopsy showed evidence of segmental to near-total tuft sclerosis with shrunken capillary tufts in light microscopy (Fig. 2). About 20% of the sampled cortex had interstitial fibrosis with tubular atrophy. Scattered hyaline and coarse granular casts were seen in the tubular lumen. Arterioles showed focal vacuolization in smooth muscle cells of media. In immunofluorescence microscopy, there was immunoglobulin M and C3 segmental entrapment. In



**Figure 1:** Brain magnetic resonance imaging. (a) Sagittal section showing thinning of corpus callosum, empty sella, and cerebellar atrophy. (b) Diffuse bilateral cerebral atrophy along with bilateral optic atrophy. (c) T2 FLAIR image showing bilateral periventricular white matter hyperintensity also involving centrum semi-ovale and corona radiata

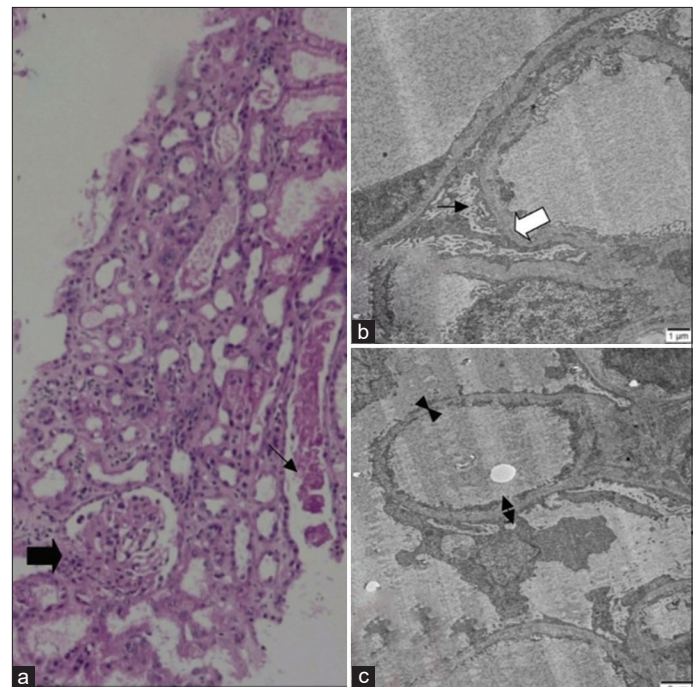
electron microscopy, there was diffuse effacement of foot processes of visceral epithelial cells, focal glomerular basement membrane subendothelial rarefaction and wrinkling of capillaries, and focal microvillous change of terminal processes of visceral epithelial cells along with electron-lucent vacuolar inclusions in the cytoplasm of few tubular cells but no electron-dense or organized deposits.

Whole-genome sequencing was done using illumine next-generation sequencing (NGS), which revealed homozygous mutation c.137 A>C (p.Glu46Ala) in the NUP85 gene in exon 3 of the long arm of chromosome 17 (17q25) which resulted in amino acid substitution from glutamic acid to alanine.

The patient was started on tacrolimus, but even after 2 months of therapy with trough level (T0) monitoring, there was no remission. Her repeat 24 h urine protein was 3.9 g/24 h, repeat USG showed contracted kidneys with altered corticomedullary differentiation. Her serum urea and creatinine were rising gradually, hence, dialysis was initiated. Within 2 weeks of dialysis initiation, the patient developed high-grade fever and her blood culture revealed coagulase-negative staphylococcus. Despite giving adequate supportive treatment and intravenous antibiotics, the child died of septic shock.

## DISCUSSION

GMS represents a clinically and genetically heterogeneous group of disorders, hence, affected individuals will not have all the symptoms and each patient will be unique [4].



**Figure 2:** Renal histopathology of the patient. (a) Light microscopy section showing segmental tuft sclerosis and shrunken capillary tuft in the glomerulus (marked by the thick arrow), hyaline cast in the tubule (marked by the thin arrow) with cytoplasmic vacuolar changes the tubule. (b) Electron microscopy image showing diffuse effacement of foot process (thick white arrow), and focal microvillous changes of terminal processes of visceral epithelial cells. (c) Electron microscopy low-resolution image showing the varying thickness of the glomerular basement membrane



Children with GMS may have various craniofacial malformations. Microcephaly (most consistent hallmark), sloping narrow forehead, flat vertex and occiput, low-set large floppy ears, high-arched palate, micrognathia, arachnodactyly, hypertelorism, and coarse hair may be present [3,8]. Our patient had microcephaly, hypertelorism, and a high-arched palate. Children with GMS almost always have structural and functional neurological manifestations, preceding renal abnormalities [8]. Structural brain abnormalities such as malformations of cortical development, hypomyelination, cerebellar atrophy, aqueductal stenosis, hydrocephalus, and Dandy-Walker malformations are prominent [9]. The cerebral cortex may have microgyria, pachygyria, agyria, or lissencephaly. In our patient, diffuse cortical and cerebellar atrophy, widespread hypomyelination, thinning of the corpus callosum, and optic atrophy were noted [3,4]. Many patients present with developmental delay and intractable seizures with EEG showing background slowing, multifocal sharp and spike-wave discharges, and rarely hypersarrhythmia [3,10]. Our patient did not have any seizure episodes and the EEG was normal but had developmental delay, speech impairment, and intellectual impairment. The prominent ocular finding includes microphthalmos, corneal opacity, cataract, ptosis, hypoplastic iris, nystagmus, and optic atrophy [3,7]. In our patient, optic atrophy was detected. Additional symptoms include short stature, clubfoot, underdeveloped nails, flexion contractures, camptodactyly, underdeveloped thyroid, adrenal glands, and ovarian agenesis [3]. In our patient, we detected short stature with thyroid hypoplasia.

The kidney involvement in GMS can range from isolated mild non-nephrotic range proteinuria to overt steroid-resistant nephrotic syndrome with rapid progression to end-stage renal disease in a span of few months [6]. Most of the patients become symptomatic within the first few months of life, at an average of 3 months, but some children present later on during childhood [9,11]. If the renal manifestations occur early, the brain formation and migration anomalies become more severe, and the patient usually dies early [5,10]. In our case, the child presented late, at the age of 9 years with the nephrotic syndrome that did not respond to the conventional steroid therapy. Pathologically, we can get a variety of renal findings. In children presenting within 6 months of age, diffuse mesangial sclerosis, focal sclerosis, and mesangial proliferation are more common, while in late presenters, we find focal glomerulosclerosis, minimal change disease, and diffuse mesangial sclerosis, interstitial fibrosis with tubular atrophy [2-4,11]. In our case, the renal biopsy is suggestive of focal segmental glomerulosclerosis with tubular atrophy and interstitial inflammation.

GMS is consistent with autosomal recessive inheritance. Recently, various mutations have been identified, the most significant among them is the WDR73 mutation. Other novel causative mutations include the genes encoding four KEOPS subunits: OSGEP, TP53RK, TPRKB, and LAGE3. In addition, NUP 107, NUP 133, and WHAMM gene mutations are also associated [6,7]. In our patient, we detected homozygous mutation in NUP 85 gene.

NUP85 gene encodes for the protein nuclear pore complex (NPC) (Nup85). It is an essential component of the Nup 107–160 subunit of the NPC [12]. NPCs are large channels spanning the nuclear envelope and mediate nucleocytoplasmic transport. There are about 30 proteins in the NPC which are coded by various NUP genes such as NUP 37, NUP 43, NUP 85, NUP 98, NUP 107, NUP 133, and NUP 210 [13]. Nup 85 plays an important role in RNA export and spindle assembly during mitosis [14]. Mutations in Nup 85, Nup 107, and Nup 133 are associated with steroid-resistant nephrotic syndrome and the latter two are also associated with GMS [7,15].

## CONCLUSION

Our case is GMS in which the onset of nephrotic syndrome is delayed, while most of the reported cases have early-onset nephrotic syndrome. The patient's kidney function rapidly worsened in a span of 3 months making her dialysis dependent and finally resulted in her death. The rapidly progressing late-onset nephrotic syndrome together with thyroid hypoplasia and homozygous mutation of NUP85 makes our case unique and could be a new variant of GMS.

## AUTHORS' CONTRIBUTIONS

All the authors contributed to the concept and design of the study.

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