

CASE REPORT

Nephrological problems in a child with Aicardi-Goutières syndrome

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ABSTRACT

Aicardi-Goutières syndrome (AGS) is a rare genetic disorder characterized by excessive interferon-alpha production, leading to central nervous system damage, manifesting as subacute encephalopathy in infancy. Moreover, the phenotype includes frostbite-like skin lesions, hepatosplenomegaly, and endocrinopathies. Here we report a case of a patient with this syndrome and a concurrent urinary system malformation.

A 3-year-old boy with AGS was referred to the nephrology clinic due to recurrent urinary tract infections. Diagnostics including voiding cystourethrography and renal scintigraphy revealed left-sided grade III vesico-ureteral reflux and minor post-inflammatory lesions. Subsequent cystometry indicated subvesical obstruction, and posterior urethral valves were incised during cystoscopy. Since the initiation of treatment with furazidine, doxazosin and oxybutynin hydrochloride, the urinary tract infection has not recurred.

Urinary system anomalies are a common issue in genetic syndromes. To date, urinary tract abnormalities have not been described as a part of the AGS phenotype.

KEY WORDS:

urinary tract infection, Aicardi-Goutières syndrome, congenital anomalies of kidney and urinary syndrome.

INTRODUCTION

Aicardi-Goutières syndrome (AGS) is an extremely rare autoimmune disorder characterized by excessive production of interferon-alpha (IFN- α). This disease is associated with mutations in one of the genes *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR1*, *IFIH1*, *LSM11*, *RNU7-1*, which usually are inherited in an autosomal recessive pattern, but in individual cases inheritance can be autosomal dominant [1–4]. All

patients with AGS exhibit symptoms resulting from damage to the nervous system [5]. Subacute encephalopathy, which develops over several months, is characterized by delay or regression of psychomotor development, feeding difficulties, aseptic fever, and irritability [6]. Subsequently, spastic paralysis of the limbs, axial hypotonia, microcephaly, and epilepsy appear, leading to severe intellectual, linguistic, and motor disability in up to 73.7% of children [3, 7]. In radiological examinations, the most frequently observed abnormalities are intracranial calcifications,

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leukodystrophy, white matter cysts, and brain atrophy [8]. Frostbite-like skin lesions characteristic for this syndrome have also been described [9]. The clinical course of this disease is highly heterogeneous. Other phenotypic features reported in the literature include endocrinopathies (hypothyroidism and diabetes insipidus are the most common), hepatosplenomegaly with increased transaminase activity [8], hematological disorders [10], cardiomegaly, and glaucoma [11]. Nephrological manifestations, most commonly described as glomerulopathies including focal segmental glomerulosclerosis, have also been reported in patients with AGS [12]. The aim of this study is to describe a case of a boy with AGS and a complex urinary system malformation.

CASE REPORT

A 3-year-old boy with a *de novo* mutation in the *IFIH1* gene confirming AGS was referred to the nephrology outpatient clinic due to recurrent urinary tract infections (UTIs). Due to regression in psychomotor development, whole exome sequencing (WES) was performed in the boy, which detected a potentially pathogenic variant of the *IFIH1* (c.1471C>A) gene. The test did not show the presence of the variant in both parents, so it arose *de novo*, indicating its pathogenic nature. Over a period of 10 months, the boy experienced six UTI episodes with fever, caused by *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella oxytoca*, treated in accordance with antibiogram results using oral amoxicillin with clavulanic acid, cefuroxime, and trimethoprim-sulfamethoxazole. Moreover, due to episodic constipation, the parents occasionally had to administer glycerin suppositories to the boy, without the need for further escalation of treatment or manual assistance during bowel movements. Despite his

age, the patient did not report any physiological needs and was diapered. According to the parents, the stream of urine was continuous and uninterrupted. The child urinated spontaneously, and the parents did not observe continuous urine leakage or abdominal pressure during micturition. In the physical examination, apart from typical AGS neurological symptoms (such as reduced axial muscle tone or spastic limb contractures) and skin changes (reddening of the distal parts of the hands), a narrow prepuce with visible urethral meatus, and retractile testicles, no significant abnormalities were observed. The patient's height was 88 cm (1st percentile), weight 11 kg (1st percentile), and body mass index 14.2 kg/m² (12th percentile) [13]. Laboratory tests revealed normocytic anemia (Hb 10.8 g/dl; RBC $3.93 \times 10^6/\mu\text{l}$; HCT 31.8%; MCV 80.9 fl), and neutropenia ($0.92 \times 10^3/\mu\text{l}$). Other blood components (PLT $327 \times 10^3/\mu\text{l}$; WBC $7.25 \times 10^3/\mu\text{l}$), renal function indicators (creatinine: 0.27 mg/dl; urea 17.8 mg/dl; GFR according to the Schwartz formula – 134.6 ml/min/1.73 m² [14]) and the ionogram remained within normal limits. An abdominal ultrasound with a particular assessment of the urinary tract showed duplication of the pyelocalyceal system of the left kidney, slight enlargement of the lower pelvis with thickening of its walls, and a visible left ureter. Voiding cystourethrography revealed the existence of a left-sided grade III vesicoureteral reflux (Figure 1). Technetium-99m ethylene dicysteine (EC) renal scintigraphy showed minor post-inflammatory scars in the upper pole of the right kidney and a cyst or focal lesion in the left kidney's hilum. In cystometry, during the filling phase, a reduced bladder volume (52 ml) and loss of compliance with detrusor instability (detrusor contractions up to 80 cm H₂O with dribbling urine leakage) were observed. During voiding with a 6 French urethral catheter, maximal detrusor pressure



FIGURE 1. Voiding cystourethrography: active grade III vesicoureteral reflux on the left side, smooth-contoured urinary bladder, normal urethra

was 106 cm H₂O with sphincter relaxation. After voiding, 11 ml of urine remained in the bladder. There was no evidence of increased electromyogram activity consistent with detrusor-external sphincter dyssynergia, and thus the co-occurrence of a neurogenic bladder was ruled out. An anatomical obstruction was suspected, and the patient underwent cystoscopy (Figure 2). Small posterior urethral valves were incised, and a membrane partially covering the external urethral orifice was revealed. The patient was scheduled for a meatoplasty procedure and started doxazosin and oxybutynin hydrochloride treatment. Follow-up cystometry was planned after the procedure, but it has not been performed so far. Since his first visit to the nephrology outpatient clinic, the patient has been receiving prophylactic doses of furazidin and no further urinary tract infections have been observed. Additionally, due to a narrow and difficult-to-retract prepuce, using steroid ointment was recommended for 4–6 weeks. Currently, the boy does not require anti-constipation treatment or manual assistance during bowel movements. The patient is scheduled to receive baricitinib treatment for the underlying disease, as a part of the Emergency Access to Drug Technologies program.

DISCUSSION

Next-generation sequencing (NGS) confirmed that the patient had a *de novo* mutation in the *IFIH1* (IFN induced with helicase C domain 1) gene. This gene, located on chromosome 2 in the 2q24.2 region, is responsible for synthesis of the cytoplasmic MDA5 protein (melanoma differentiation-associated gene 5) [1]. This protein enables the detection of viral genetic material, particularly double-stranded RNA, which leads to the activation of IFN [15]. This cascade inhibits viral replication and stimulates the cell-mediated immune response [16].

So far, several mutations of the *IFIH1* gene have been found in patients with AGS, all inherited in an autosomal dominant pattern [1]. Each of these mutations led to the production of the hyperactive MDA5 protein, which caused excessive production of IFN- α and thus initiated an autoimmune reaction [15]. Patients with a confirmed *IFIH1* mutation manifest typical symptoms of neonatal and infantile AGS with increased cerebrospinal fluid IFN- α activity or increased expression of INF-stimulated genes [1, 15]. Most patients in infancy present axial hypotonia, spasticity, and delayed psychomotor development. Imaging studies show calcifications of the basal ganglia, brain tissue atrophy, and abnormalities in the white matter [1].

It is important to highlight that to the best of our knowledge there are no reports of coexisting urinary tract malformations in AGS patients. This may be a consequence of the rarity of this syndrome and the variability of its phenotype. This study aimed to expand knowledge on this disease by presenting a case of a patient with AGS accompanied by a urinary system defect.

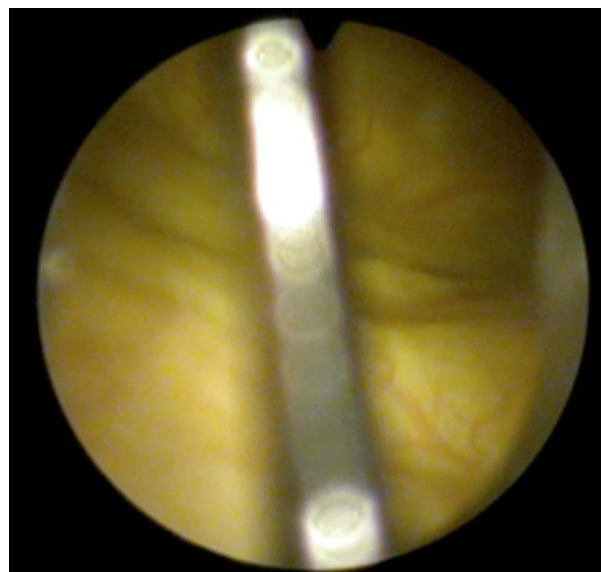


FIGURE 2. Cystoscopy: prominent trabeculation of the urinary bladder wall

Congenital anomalies of the kidney and urinary tract (CAKUT) are among the most common congenital defects in children, occurring in as many as 1 in 200 live births [17]. They are often seen in co-occurrence with other developmental defects and genetically conditioned diseases [18]. Current literature does not describe CAKUT as part of the AGS phenotype; therefore it is possible that the co-occurrence of a posterior urethral valve in this patient might be only a coincidence. However, there are studies describing the coexistence of AGS with other kidney structure and function disorders. Wang *et al.* [5] gathered in 2022 clinical data on 20 children affected by AGS, observing significant kidney structure abnormalities in three patients. Chronic interstitial changes were demonstrated in two of them, and a kidney biopsy of the third patient showed membranous nephropathy. He *et al.* [19] reported an 11-year-old girl with an *RNASEH2B* mutation confirmed by whole exome sequencing (WES), exhibiting symptoms of the AGS, lymphopenia, increased inflammatory markers, presence of rheumatoid factor and anti-cyclic citrullinated peptide antibodies (anti-CCP), and low complement levels. Additionally, increased renal function parameters and chronic elevation of β_2 -microglobulin in urine were observed. Kidney biopsy showed glomerulosclerosis (in 3/14 glomeruli), interstitial fibrosis with tubular atrophy, and infiltration by lymphocytes and other mononuclear cells. No presence of amyloid, immune complexes, or complement components was observed in immunohistochemical staining. Other authors suggested that renal damage might result directly from the *RNASEH2B* mutation and consequent increased IFN- α levels in renal tubule cells or secondarily to systemic, chronic inflammation [20]. Additionally, individual cases of focal segmental glomerulosclerosis in AGS patients have been described [12]. Lodi *et al.* [21] identified the negative impact of increased IFN- α concentration on the kidneys,

with pathological features including podocyte loss, capillary loop collapse, and proliferation of Bowman's capsule epithelial cells. Such abnormalities are observed in type 1 interferonopathies such as AGS, vascular disease related to mutations inducing INF production, and even in therapy with recombinant INF.

The multitude of genes involved in urinary system embryogenesis makes CAKUT a common manifestation of numerous genetic syndromes. The spectrum of defects varies, including renal hypodysplasia and vesicoureteral reflux, ureteral stenosis, and in boys, posterior urethral valves [17]. In the described patient, the indications for diagnostics of the urinary system were recurrent infections and an abnormal image of the urinary tract in ultrasound examination (in accordance with the recommendations of the Polish Society of Pediatric Nephrology; PTNFD [22]). Voiding cystourethrography revealed left-sided vesicoureteral reflux. In children with recurrent UTIs and high-grade reflux, cystometric study is recommended, which, in this case, indicated the possibility of a subvesical obstruction. Cystoscopy enabled the diagnosis and treatment of posterior urethral valves. Unilateral vesicoureteral reflux (VUR) may occur in up to 35% of boys with a posterior urethral valve [23]. The presence of VUR depends on two factors: the pressure in the urinary tract and the anatomical position of the ureters inside or outside the bladder triangle. The existence of a genetic syndrome predisposes to defects of the urinary system. Therefore, in such patients, diagnosis should not be postponed due to the existing burden. In AGS, all infections can have a severe course, worsening the underlying disease and negatively affecting the neurological status of the patient.

Considering the possibility of renal dysfunction in patients with AGS and, as shown in the above case, urinary system defects and infections, we believe that these patients should undergo periodic nephrological evaluation. Suggested examinations include assessment of creatinine or cystatin C levels (considering possible muscle atrophy), urine analysis, blood pressure monitoring, and ultrasonography. If symptoms suggest the possibility of UTIs (e.g., fever of unknown origin), urinalysis and urine culture are necessary.

Treating AGS is a therapeutic challenge due to its incurable nature and high mortality rate among children (19.3%) [3]. This requires an interdisciplinary approach focused on symptom alleviation. Research on new drugs aimed at reducing the production and/or signaling inhibition of IFN- α is ongoing. Promising results involve the use of Janus kinase (JAK) inhibitors (such as baricitinib and ruxolitinib) and reverse transcriptase inhibitors (RTIs) [8].

CONCLUSIONS

Recurrent urinary tract infections always require comprehensive diagnostics for urinary system defects and functional disorders, regardless of coexisting conditions.

Patients with AGS require multidisciplinary care, including nephrological management with periodic assessment of the urinary tract structure and function due to the potential co-occurrence of disorders in this system.

DISCLOSURES

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REFERENCES

1. Rice GI, Del Toro Duany Y, Jenkins EM, et al. Gain-of-function mutations in IFIH1 cause a spectrum of human disease phenotypes associated with upregulated type I interferon signaling. *Nat Genet* 2014; 46: 503-509.
2. Liu A, Ying S. Aicardi-Goutières syndrome: a monogenic type I interferonopathy. *Scand J Immunol* 2023; 98: e13314. DOI: 10.1111/sji.13314.
3. Crow YJ, Chase DS, Schmidt JL, et al. Characterization of human disease phenotypes associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR, and IFIH1. *Am J Med Genet A* 2015; 167A: 296-312.
4. Ugenti C, Lepelley A, Depp M, et al. cGAS-mediated induction of type I interferon due to inborn errors of histone pre-mRNA processing. *Nat Genet* 2020; 52: 1364-1372.
5. Wang W, Wang W, He TY, et al. Analysis of clinical characteristics of children with Aicardi-Goutières syndrome in China. *World J Pediatr* 2022; 18: 490-497.
6. D'arrigo S, Riva D, Bulgheroni S, et al. Aicardi-Goutières syndrome: description of a late onset case. *Dev Med Child Neurol* 2008; 50: 631-634.
7. Livingston JH, Lin JP, Dale RC, et al. A type I interferon signature identifies bilateral striatal necrosis due to mutations in ADAR1. *J Med Genet* 2014; 51: 76-82.
8. Dell'Isola GB, Dini G, Culpepper KL, et al. Clinical spectrum and currently available treatment of type I interferonopathy Aicardi-Goutières syndrome. *World J Pediatr* 2023; 19: 635-643.
9. Kolivras A, Aeby A, Crow Y, et al. Cutaneous histopathological findings of Aicardi-Goutières syndrome, overlap with chilblain lupus. *J Cutan Pathol* 2008; 35: 774-778.
10. Adang LA, Gavazzi F, D'Aiello R, et al. Hematologic abnormalities in Aicardi Goutières syndrome. *Mol Genet Metab* 2022; 136: 324-329.
11. Rice G, Patrick T, Parmar R, et al. Clinical and molecular phenotype of Aicardi-Goutières syndrome. *Am J Hum Genet* 2007; 81: 713-725.
12. Fenaroli P, Rossi GM, Angelotti ML, et al. Collapsing glomerulopathy as a complication of type I interferon-mediated glomerulopathy in a patient with RNASEH2B-related Aicardi-Goutières syndrome. *Am J Kidney Dis* 2021; 78: 750-754.
13. Kułaga Z, Grajda A, Gurzkowska B, et al. Polish 2012 growth references for preschool children. *Eur J Pediatr* 2013; 172: 753-761.
14. Schwartz GJ, Muñoz A, Schneider ME, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009; 20: 629-637.
15. Oda H, Nakagawa K, Abe J, et al. Aicardi-Goutières syndrome is caused by IFIH1 mutations. *Am J Hum Genet* 2014; 95: 121-125.
16. Asgari S, Schlapbach LJ, Anchisi S, et al. Severe viral respiratory infections in children with IFIH1 loss-of-function mutations. *Proc Natl Acad Sci U S A* 2017; 114: 8342-8347.

17. Murugapoopathy V, Gupta IR. A primer on congenital anomalies of the kidneys and urinary tracts (CAKUT). *Clin J Am Soc Nephrol* 2020; 15: 723-731.
18. Stoll C, Dott B, Alembik Y, Roth MP. Associated nonurinary congenital anomalies among infants with congenital anomalies of kidney and urinary tract (CAKUT). *Eur J Med Genet* 2014; 57: 322-328.
19. He T, Xia Y, Yang J. Systemic inflammation and chronic kidney disease in a patient due to the RNASEH2B defect. *Pediatr Rheumatol Online J* 2021; 19: 9. DOI: 10.1186/s12969-021-00497-2.
20. Bocci V, Pacini A, Muscettola M, et al. Renal filtration, absorption and catabolism of human alpha interferon. *J Interferon Res* 1981; 1: 347-352.
21. Lodi L, Mastrolia MV, Bello F, et al. Type I interferon-related kidney disorders. *Kidney Int* 2022; 101: 1142-1159.
22. Wasilewska A (red.). Zalecenia Polskiego Towarzystwa Nefrologii Dziecięcej (PTNFD) dotyczące postępowania z dzieckiem z zakażeniem układu moczowego. Uniwersytet Medyczny w Białymstoku, Białystok 2021; pp. 1-77.
23. Atobatele M, Oyinloye O, Nasir A, et al. Posterior urethral valve with unilateral vesicoureteral reflux and patent urachus: a rare combination of urinary tract anomalies. *Urol Ann* 2015, 7: 240-243.