Urological Problems in Patients with Menkes Disease

Mi Young Kim, Ji Hyun Kim, Myung Hyun Cho, Young Hun Choi, Seong Heon Kim, Young Jae Im, Kwanjin Park, Hee Gyung Kang, Jong-Hee Chae, and Hae Il Cheong

Background: Menkes disease (MD) is a rare X-linked hereditary multisystemic disorder that is caused by dysfunction of copper metabolism. Patients with MD typically present with progressive neurodegeneration, some connective tissue abnormalities, and characteristic “kinky” hair. In addition, various types of urological complications are frequent in MD because of underlying connective tissue abnormalities. In this study, we studied the clinical features and outcomes of MD, focusing on urological complications.

Methods: A total of 14 unrelated Korean pediatric patients (13 boys and 1 girl) with MD were recruited, and their phenotypes and genotypes were analyzed by retrospective review of their medical records.

Results: All the patients had early-onset neurological deficit, including developmental delay, seizures, and hypotonia. The girl patient showed normal serum copper and ceruloplasmin levels as well as milder symptoms. Mutational analysis of the ATP7A gene revealed 11 different mutations in 12 patients. Bladder diverticula was the most frequent urological complication: 8 (57.1%) in the 14 patients or 8 (72.7%) in the 11 patients who underwent urological evaluation. Urological imaging studies were performed essentially for the evaluation of accompanying urinary tract infections. Four patients had stage II chronic kidney disease at the last follow-up.

Conclusion: Urological problems occurred frequently in MD, with bladder diverticula being the most common. Therefore, urological imaging studies and appropriate management of urological complications, which may prevent or reduce the development of urinary tract infections and renal parenchymal damage, are required in all patients with MD.

Keywords: ATP7A Gene; Chronic Kidney Disease; Menkes Disease; Urinary Bladder Diverticula; Urological Complication
INTRODUCTION

Menkes disease (MD) is a very rare hereditary multisystemic disorder of copper metabolism with an X-linked recessive inheritance. MD is alternatively described as “kinky hair disease,” because of the characteristic sparse and steely gray or bright-colored hair of the patients. MD is caused by a defect in the ATP7A gene, which encodes a trans-membrane copper-transporting P-type ATPase, ATP7A. Defective copper transport in MD leads to malfunction of one or more copper-requiring enzymes (cuproenzymes), including lysyl oxidase, cytochrome c oxidase, tyrosinase, extracellular superoxide dismutase, and peptidylglycine α-amidating monoxygenase. The diverse clinical features of MD are attributable to the malfunction of one or more cuproenzymes.

Patients with MD typically present with progressive neurodegeneration, some connective tissue abnormalities, and characteristic “kinky” hair. Various kinds of urological complications are also frequently observed in MD, including bladder diverticula, bladder outflow obstruction, vesicoureteral reflux, renal rupture, and cryptorchidism. These conditions predispose patients with MD to recurrent urinary tract infections and renal parenchyma damage. However, systematic studies on urological complications have not been reported extensively.

In this study, we analyzed the clinical features, image findings, and outcomes of urological complications in 14 Korean pediatric patients with MD.

METHODS

A total of 14 unrelated Korean pediatric patients diagnosed with MD at Seoul National University Children’s Hospital, Seoul, Korea or Pusan National University Children’s Hospital, Yangsan, Korea between 2005 and 2017 were included in this study. The phenotypes of the patients, with focus on accompanying urologic problems, were analyzed by retrospective review of the medical records. Mutational analysis of the ATP7A gene was carried out by direct sequencing and/or multiplex ligation-dependent probe amplification. Genomic DNA was isolated from peripheral blood leukocytes. The cases of seven patients (patients 1, 3–6, 9, and 12) have already been reported.

Ethics statement

This study was approved by the Institutional Review Board (IRB) of the Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Korea (IRB No. 1408-010-599). The parents of the patients provided informed consent to participate in this study.

RESULTS

Initial presentation of the patients

Among the 14 patients, 13 were boys and one (patient 14) was a girl. The median gestational period and birth weight were 38 weeks (ranges, 36–41 weeks) and 3.06 kg (ranges, 2.50–3.80 kg), respectively. None of the patients had any serious perinatal problems. All the patients presented with neurologic deficits, including developmental delay (n = 7), seizures (n = 6), and hypotonia (n = 3). The onset age was within 4 months after birth in 12 patients, while the remaining two patients, one without a pathogenic mutation and the other being the...
girl patient, presented with developmental delay at the age of 10 months and 13 months, respectively. The initial serum copper level was available for 11 patients, with a median value of 17.5 μg/dL (ranges, 7–66 μg/dL; normal, 65–140 μg/dL). The initial serum ceruloplasmin level (n = 10) was ≤ 10 mg/dL (normal, 15–40 mg/dL) in all patients except the girl patient, who had normal initial serum copper and ceruloplasmin levels (Table 1).

**Mutational analyses of the ATP7A gene**
Mutational study of the ATP7A gene was performed for 13 patients, and it revealed 11 different pathogenic mutations in 12 patients, including 4 large deletions, 2 missense mutations, 2 nonsense mutations, 2 frame-shifting short deletions, and 1 abnormal splicing mutation. Seven mutations were novel. No mutation was detected in patient 6, and the mutational study was not done for patient 12. Family history of MD was negative in all patients except one (patient 7), who had an affected younger brother. Genetic testing was performed on the family members of the patients, and the mother of patients 7 was found to be heterozygous carrier of the mutation found in her son (Table 1).

**Urological problems**
Imaging studies of the kidney and urinary tract were performed for 11 patients (patients 1–11), and bladder diverticula was the most common finding detected in eight patients (patients 1–8) (Fig. 1A). Neurogenic bladder dysfunction was noted in two patients (patients 6 and 7). In patient 6, ultrasonography revealed diffuse wall thickening of the urinary bladder (UB) with multiple bladder diverticula (Fig. 1B), and a urodynamic study revealed neurogenic overactivity of the detrusor muscle and synergic sphincter muscle without vesicoureteral reflux. Imaging studies of patient 7 revealed bilateral vesicoureteral reflux on voiding cystourethrogram and diffuse wall thickening of the UB with bladder diverticulum on ultrasonography. However, an urodynamic study was not performed in patient 7 due to lack of parental consent. Bilateral hydrourerter was detected in patient 3, and small renal cortical scar on the left upper pole of the kidney was detected on technetium-99m dimercapsuccinic acid renal scan in patient 2. The imaging studies (n = 8) were performed chiefly as part of a diagnostic work-up for concomitant urinary tract infections. Urinary tract infections developed recurrently in three patients. Two patients received urological treatment: patient 6, who had severe neurogenic bladder dysfunction, underwent bladder diverticulectomy at the age of 5 years, and patient 7, who had bilateral vesicoureteral reflux and 19 episodes of urinary tract infection, underwent ureteroneocystostomy at the age of 1 year.

### Table 1. Phenotypes and genotypes of the patients

| Pt | GA, wk | BWt, kg | Initial symptoms | Onset, months | ATP7A mutations | Serum copper, μg/dL | Serum ceruloplasmin, mg/dL |
|----|--------|---------|-----------------|--------------|-----------------|---------------------|---------------------------|
| 1  | 37     | 2.50    | Seizure         | 3            | Exon 6–7 deletion<sup>a</sup> | 12.9                | <7                        |
| 2  | 38     | 3.10    | DD              | 4            | c.1303delA, p.A434Qfs<sup>*2</sup> | 16.2                | <7                        |
| 3  | 39<sup>*</sup> | 3.80    | Seizure         | 4            | c.2179G>A, p.G727R | 36.1                | <7                        |
| 4  | 38     | 2.80    | DD              | 3            | c.2446C>T, p.Q816<sup>*</sup> | 24.5                | 10.0                      |
| 5  | 37     | 2.70    | Seizure, DD     | 3            | c.2179G>A, p.G727R | 15.0                | <8.6                      |
| 6  | 40     | 3.43    | DD              | 10           | Not detected    | 17.5                | <8                        |
| 7  | 37     | 3.07    | Seizure         | 3            | Exon 19–21 deletion<sup>a</sup> | 7.0                 | 6.0                       |
| 8  | 36<sup>1</sup> | 3.50    | Hypotonia       | At birth     | c.2627-2A>G<sup>a</sup> | 11.18               | 6.7                       |
| 9  | 38     | 3.29    | DD, hypotonia   | 3            | c. 601C>T, p.R201<sup>*</sup> | NA                  | NA                        |
| 10 | 38     | 2.50    | Seizure         | 3            | Exon 3–23 deletion | 20.5                | <7                        |
| 11 | 36<sup>3</sup> | 2.54    | Hypotonia       | 4            | Exon 16 deletion<sup>a</sup> | NA                  | NA                        |
| 12 | 39<sup>*</sup> | 3.50    | DD              | 3            | Not done        | 32.5                | NA                        |
| 13 | 37     | 3.04    | Seizure         | 3            | c.3335delA, p.Q1112Rfs<sup>*26</sup> | NA                  | NA                        |
| 14b| 41     | 3.32    | DD              | 13           | c.40148G>A, p.E1350K<sup>a</sup> | 66.0                | 19.3                      |

Pt = patient, GA = gestational age, BWt = birth weight, DD = developmental delay, NA = not available.
<sup>a</sup>Novel mutations; <sup>*</sup>Girl patient.
Other organ manifestations that were detected were pectus excavatum (n = 6), inguinal hernia (n = 5), intracranial hemorrhage/cephalhematoma (n = 4), hip dislocation (n = 2), and diaphragmatic hernia (n = 1) (Table 2).

Table 2. Associated abnormalities in the urinary tract and other organs

| Pt | No. of UTI | No. of bladder diverticula (detection age in months) | Other urologic abnormalities | eGFRc | Other organ abnormalities | Current status (age in months) |
|----|------------|-----------------------------------------------------|------------------------------|-------|--------------------------|-------------------------------|
| 1  | 2          | > 3 (6)                                              | None                         | 118   | Pectus excavatum          | Survived (75)                |
|    |            |                                                     |                              |       | Inguinal hernia           |                               |
|    |            |                                                     |                              |       | Failure to thrive         |                               |
| 2  | 1          | > 3 (4)                                              | Renal cortical scar on left kidney upper pole on DMSA renal scan | 75    | Inguinal hernia           | Survived (5)                 |
|    |            |                                                     |                              |       | Cephalhematoma            |                               |
| 3  | 1          | > 3 (102)                                            | Hydroureter                  | 128   | Epidural hematoma         | Died (133)                   |
|    |            |                                                     |                              |       | Pectus excavatum          |                               |
|    |            |                                                     |                              |       | Wormian bones             |                               |
|    |            |                                                     |                              |       | Cephalhematoma            |                               |
| 4  | 3          | 2 (35)                                              | None                         | 136   | Inguinal hernia           | Died (121)                   |
|    |            |                                                     |                              |       | Hip dislocation           |                               |
| 5  | 1          | > 3 (12)                                             | None                         | 83    | Pectus excavatum          | Lost to F-U (38)             |
|    |            |                                                     |                              |       | Inguinal hernia           |                               |
| 6  | 1          | 3 (54)                                              | Neurogenic bladder*          | 74    | Pectus excavatum          | Survived (83)                |
|    |            |                                                     |                              |       | Failure to thrive         |                               |
|    |            |                                                     |                              |       | Hip dislocation           |                               |
| 7  | > 3        | 1 (27)                                              | Vesicoureteral reflux*       | Unknown | Pectus excavatum         | Survived (74)                |
|    |            |                                                     | Neurogenic bladder           |                              |                            |                               |
| 8  | 1          | > 3 (17)                                             | None                         | Unknown | Subdural hematoma        | Lost to F-U (22)             |
| 9  | 1          | 0                                                   | None                         | 116   | Pectus excavatum          | Lost to F-U (29)             |
|    |            |                                                     |                              |       | Inguinal hernia           |                               |
|    |            |                                                     |                              |       | Failure to thrive         |                               |
| 10 | 0          | 0                                                   | None                         | 129   | None                      | Lost to F-U (9)              |
| 11 | 0          | 0                                                   | None                         | 72    | None                      | Lost to F-U (8)              |
| 12 | 0          | Not evaluated                                       | Not evaluated                | 111   | Cephalhematoma            | Lost to F-U (10)             |
| 13 | 0          | Not evaluated                                       | Not evaluated                | Unknown | Diaphragmatic hernia     | Survived (6)                 |
| 14 | 0          | Not evaluated                                       | Not evaluated                | 146   | None                      | Survived (84)                |

Pt = patients, UTI = urinary tract infection, DMSA = technetium-99m dimercaptosuccinic acid renal scan, F-U = follow-up.

*Bladder diverticulectomy was done; **Ureteroneocystostomy was done; *Estimated glomerular filtration rate calculated by the revised Schwartz equation (mL/min/1.73 m²).
Disease course and prognosis

All patients had neurodevelopmental delay of various severity levels, and 11 patients took long-term antiepileptic drugs because of intractable seizures. Two patients (patients 8 and 14) were treated with periodic subcutaneous injections of copper-histidine, but the treatment did not affect the overall disease course. Five patients underwent tracheostomy and percutaneous endoscopic gastrostomy, and one other patient needed a nasal biphasic positive airway pressure support.

Two patients died at the ages of 10 and 11 years, respectively, at the end of palliative care at home, and six patients were lost to follow-up at a median age of 16 months (ranges, 8–38 months). The median current age of four surviving patients was 75 months (ranges, 5–83 months). The median estimated glomerular filtration rate (calculated by the revised Schwartz equation, n = 11) at the last follow-up was 118 mL/min/1.73 m² (ranges, 72–327). Four patients had stage II chronic kidney disease (Table 2).

DISCUSSION

MD is a lethal multisystemic disorder of copper metabolism, presenting with progressive neurodegeneration and connective tissue disturbances, together with characteristic “kinky” hair, as the main manifestations.\(^1\)\(^-\)\(^3\) MD is inherited as an X-linked recessive trait and therefore the vast majority of patients are men. There was one girl patient (patient 14) in our study, who showed normal initial serum copper and ceruloplasmin levels and had milder symptoms and older age onset than the boy patients. The clinical symptoms of MD in girl are caused by skewed inactivation of the X chromosome that harbors the mutation\(^15\) or translocation between the X chromosome and an autosome.\(^16\) Patient 14 in our study had a missense mutation in \(ATP7A\), without evidence of chromosomal translocation.

Patients usually present with early-onset neurodevelopmental delay and uncontrolled intractable seizures. The neurological deficits are all irreversible, and most of the severely affected patients died before the third year of life.\(^3\) Patients in this study also showed similar poor prognosis.

MD is caused by mutations in the \(ATP7A\) gene.\(^17\)\(^-\)\(^21\) To date, 354 disease-causing or potentially disease-causing mutations in \(ATP7A\) have been reported (HGMD\(^6\) Professional 2018.2, https://portal.biobase-international.com/hgmd/pro/start.php) in association with MD or its variant phenotypes: missense/nonsense mutations, 114 (32%); splicing substitutions, 69 (19%); gross deletions, 65 (18%); small deletions, 58 (16%); and others. The mutations are distributed almost equally throughout the gene, without any hot spot. In our study, large deletions were the most common of the mutations.

Urologic complications are frequent in MD, with bladder diverticula being the most common one.\(^13\) The ATP7A protein is an energy-dependent, transmembrane protein that is involved in the delivery of copper to the secreted copper enzymes and in the export of surplus copper from the cells. Defective cellular copper transport in MD leads to altered activity of various kinds of cuproenzymes and the consequent diverse phenotypes of MD.\(^12\) Lysyl oxidase, a copper-dependent and elastic-fiber-associated cuproenzyme, is known to be responsible for lysine-derived cross-linking of collagen and elastin in connective tissue. Defective function of lysyl oxidase in MD results in an altered elastic-fiber morphology, which leads to arterial
tortuosities, bladder diverticula and other elastic tissue pathologies, including premature rupture of fetal membranes, cephalohematoma, subdural hematoma, abnormal facies, high-arched palate, emphysema, hernias, loose skin and joints, osteoporosis, petechial hemorrhage, poor wound healing, and central nervous system degeneration. In 2006, Zaffanello et al. performed a retrospective review of 57 cases of MD, including 55 published case reports and two of their own cases, focusing on urological complications. They reported that the prevalence of bladder diverticulum was 38.6% of the total number of patients. However, most of the reports that they reviewed did not focus specifically on urological complication and therefore the prevalence of urological complications may have been underestimated. In addition, urological imaging studies are usually performed only in patients with urological problems, including urinary tract infections, voiding problems, etc. Therefore, urological complications are more likely to be found in older patients with longer follow-up periods. In fact, Zaffanello et al. reported that the number of urological complications increased progressively with the age of the patients. The prevalence of urological complications in our study was high: 8 (57.1%) of a total of 14 patients or 8 (72.7%) of 11 patients in whom urological evaluation was performed, which may be closer to the actual prevalence. A longitudinal cohort study, rather than a cross-sectional study, is needed to clarify this issue.

The diverticula in MD are usually multiple and vary in size and location, as shown in our study. Although the pathogenesis of bladder diverticula in MD has not been fully elucidated yet, it may result from impaired elasticity of the bladder muscle layer, caused by lysyl oxidase dysfunction, as well as disturbed innervation of the bladder in association with severe progressive neurodegenerative changes. In our study, two patients had neurogenic bladder dysfunction. Since lysyl oxidase activity cannot be corrected by parenteral copper administration, connective tissue laxity and the progression of urological complications cannot be completely improved. However, Zaffanello et al. showed that the progression of urological complications may be delayed with copper treatment. In our study, only two patients (patients 8 and 14) were treated with parenteral copper: patient 8 demonstrated bladder diverticula on imaging studies performed at the age of 17 months after an episode of urinary tract infection, and patient 14, a girl patient with a mild phenotype, did not undergo urological imaging studies because of the absence of urinary tract infection.

Bladder diverticula result in urinary stasis with a high residual urine volume, which leads to infections and further bladder dysfunction. Therefore, the main goal of management in patients with bladder diverticula is to accomplish complete bladder emptying with clean intermittent catheterization or open surgical drainage in severe cases. Two of our patients underwent urological intervention. However, because of its rarity, no consensus on the treatment of bladder diverticula in patients with MD is available. Furthermore, whether surgical treatment is warranted given the propensity of bladder diverticula to recur and the generally short expected life span of these patients remains to be elucidated. Therefore, surgical intervention should be considered based on the clinical condition of each patient, including the severity of urological problems, expected life expectancy, and tolerance to general anaesthesia.

In conclusion, urological complications are very frequent in MD, with bladder diverticula being the most common. Bladder diverticula predispose patients with MD to urinary stasis, recurrent urinary tract infections, and renal parenchymal damage. Therefore, urological imaging studies and appropriate management of urological complications are required in all patients with MD.
REFERENCES

1. Menkes JH, Alter M, Steigleder GK, Weakley DR, Sung JH. A sex-linked recessive disorder with retardation of growth, peculiar hair, and focal cerebral and cerebellar degeneration. Pediatrics 1962;29(5):764-79.

2. Danks DM, Campbell PE, Walker-Smith J, Stevens BJ, Gillespie JM, Blomfield J, et al. Menkes’ kinky-hair syndrome. Lancet 1972;1(7760):1100-2.

3. Tümer Z, Möller LB. Menkes disease. Eur J Hum Genet 2010;18(5):511-8.

4. Vulpe C, Levinson B, Whitney S, Packman S, Gitschier J. Isolation of a candidate gene for Menkes disease and evidence that it encodes a copper-transporting ATPase. Nat Genet 1993;3(1):7-13.

5. Chelly J, Tümer Z, Tønnesen T, Petterson A, Ishikawa-Brush Y, Tommerup N, et al. Isolation of a candidate gene for Menkes disease that encodes a potential heavy metal binding protein. Nat Genet 1993;3(1):14-9.

6. Mercer JF, Livingston J, Hall B, Paynter JA, Begy C, Chandrasekharappa S, et al. Isolation of a partial candidate gene for Menkes disease by positional cloning. Nat Genet 1993;3(1):20-5.

7. El Meskini R, Culotta VC, Mains RE, Eipper BA. Supplying copper to the cuproenzyme peptidylglycine alpha-amidating monoxygenase. J Biol Chem 2003;278(14):12278-84.

8. Kodama H, Okabe I, Yanagisawa M, Kodama Y. Copper deficiency in the mitochondria of cultured skin fibroblasts from patients with Menkes syndrome. J Inherit Metab Dis 1989;12(4):386-9.

9. Petris MJ, Strausak D, Mercer JF. The Menkes copper transporter is required for the activation of tyrosinase. Hum Mol Genet 2000;9(19):2845-51.

10. Qin Z, Itoh S, Jeney V, Ushio-Fukai M, Fukai T. Essential role for the Menkes ATPase in activation of extracellular superoxide dismutase: implication for vascular oxidative stress. FASEB J 2006;20(2):334-6.

11. Royce PM, Camakaris J, Danks DM. Reduced lysyl oxidase activity in skin fibroblasts from patients with Menkes’ syndrome. Biochem J 1980;192(2):579-86.

12. Horn N, Tümer Z. Menkes disease and the occipital horn syndrome. In: Royce PM, Steinmann B, editors. Connective Tissue and Its Heritable Disorders: Molecular, Genetic, and Medical Aspects. 2nd ed. New York, NY: John Wiley and Sons Inc.; 2002, 651-85.

13. Zaffanello M, Maffeis C, Fanos V, Franchini M, Zamboni G. Urological complications and copper replacement therapy in childhood Menkes syndrome. Acta Paediatr 2006;95(7):785-90.

14. Lee JS, Lim BC, Kim KJ, Hwang YS, Cheon JE, Kim IO, et al. Menkes disease in Korea: ATP7A mutation and epilepsy phenotype. Brain Dev 2015;37(2):223-9.

15. Smkopou P, Samanta M, Berry GT, Hecht L, Engle EC, Lichter-Konecki U. Menkes disease in affected females: the clinical disease spectrum. Am J Med Genet A 2015;167A(2):417-20.

16. Möller LB, Lenartowicz M, Zabot MT, Josiane A, Burglen L, Bennett C, et al. Clinical expression of Menkes disease in females with normal karyotype. Orphanet J Rare Dis 2012;7(1):6.

17. Das S, Levinson B, Whitney S, Vulpe C, Packman S, Gitschier J. Diverse mutations in patients with Menkes disease often lead to exon skipping. Am J Hum Genet 1994;55(5):883-9.

18. Tümer Z, Möller LB, Horn N. Mutation spectrum of ATP7A, the gene defective in Menkes disease. Adv Exp Med Biol 1999;448:83-95.

19. Gu YH, Kodama H, Murata Y, Mochizuki D, Yanagawa Y, Ushijima H, et al. ATP7A gene mutations in 16 patients with Menkes disease and a patient with occipital horn syndrome. Am J Med Genet 2001;99(3):217-22.

https://jkms.org
20. Tümør Z, Birk Møller L, Horn N. Screening of 383 unrelated patients affected with Menkes disease and finding of 57 gross deletions in ATP7A. *Hum Mutat* 2003;22(6):457-64. [PUBMED](https://pubmed.ncbi.nlm.nih.gov/22357377/) | [CROSSREF](https://doi.org/10.1002/humu.10331)

21. Møller LB, Bukrinsky JT, Mølgaard A, Paulsen M, Lund C, Tümør Z, et al. Identification and analysis of 21 novel disease-causing amino acid substitutions in the conserved part of ATP7A. *Hum Mutat* 2005;26(2):84-93. [PUBMED](https://pubmed.ncbi.nlm.nih.gov/15783472/) | [CROSSREF](https://doi.org/10.1002/humu.20120)

22. Rucker RB, Kosonen T, Clegg MS, Mitchell AE, Rucker BR, Uriu-Hare JY, et al. Copper, lysyl oxidase, and extracellular matrix protein cross-linking. *Am J Clin Nutr* 1998;67(5 Suppl):996S-1002S. [PUBMED](https://pubmed.ncbi.nlm.nih.gov/9691992/) | [CROSSREF](https://doi.org/10.1093/ajcn/67.5.996)

23. Urbán Z, Boyd CD. Elastic-fiber pathologies: primary defects in assembly-and secondary disorders in transport and delivery. *Am J Hum Genet* 2000;67(1):4-7. [PUBMED](https://pubmed.ncbi.nlm.nih.gov/10644149/) | [CROSSREF](https://doi.org/10.1086/303103)

24. Harcke HT Jr, Capitanio MA, Grover WD, Valdes-Dapena M. Bladder diverticula and Menkes' syndrome. *Radiology* 1977;124(2):459-61. [PUBMED](https://pubmed.ncbi.nlm.nih.gov/847529/) | [CROSSREF](https://doi.org/10.1148/radiology.124.2.628249)

25. Kodama H, Murata Y, Kobayashi M. Clinical manifestations and treatment of Menkes disease and its variants. *Pediatr Int* 1999;41(4):423-9. [PUBMED](https://pubmed.ncbi.nlm.nih.gov/10552244/) | [CROSSREF](https://doi.org/10.1111/j.1442-200X.1999.00423.x)

26. Oshio T, Hino M, Kirino A, Matsumura C, Fukuda K. Urologic abnormalities in Menkes' kinky hair disease: report of three cases. *J Pediatr Surg* 1997;32(5):782-4. [PUBMED](https://pubmed.ncbi.nlm.nih.gov/9146630/) | [CROSSREF](https://doi.org/10.1016/S0022-3468(97)90081-4)

27. Eradi B, Rajimwale A. Excision of massive bladder diverticula in Menkes disease. *J Pediatr Urol* 2010;6(3):312-4. [PUBMED](https://pubmed.ncbi.nlm.nih.gov/20863044/) | [CROSSREF](https://doi.org/10.1016/j.jspurol.2010.05.016)

28. Kageyama S, Okada Y, Konishi T, Koizumi S, Tomoyoshi T. Menkes' kinky hair disease associated with a large bladder diverticulum: a case report. *Int J Urol* 1997;4(3):318-20. [PUBMED](https://pubmed.ncbi.nlm.nih.gov/9129521/) | [CROSSREF](https://doi.org/10.1046/j.1442-2042.1997.00141.x)

29. Hebert KL, Martin AD. Management of bladder diverticula in Menkes syndrome: a case report and review of the literature. *Urology* 2015;86(1):162-4. [PUBMED](https://pubmed.ncbi.nlm.nih.gov/25996855/) | [CROSSREF](https://doi.org/10.1016/j.urology.2014.10.049)

30. Tobias JD. Anaesthetic considerations in the child with Menkes' syndrome. *Can J Anaesth* 1992;39(7):712-5. [PUBMED](https://pubmed.ncbi.nlm.nih.gov/1237833/) | [CROSSREF](https://doi.org/10.1007/BF03011072)