Multiple Bladder Diverticula in Children with Menkes Disease: Report of Two Cases and Review of the Literature

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Abstract
Menkes disease, also known as “kinky hair disease”, Menkes syndrome and “steely hair disease”. It is a rare recessive neurodegenerative X-linked congenital disorder of copper metabolism with multisystem involvement. Various urologic abnormalities, including vesicoureteral reflux, hydronephrosis, bladder outflow obstruction, urinary tract infections, renal rupture, undescended testes and especially large and multiple bladder diverticula, are often described as part of clinical manifestation in children with Menkes disease. The presence of bladder diverticula is strictly attributed to connective tissue alterations dependent on decreased lysyl oxidase activity, which is necessary for collagen formation. We report two cases of children with Menkes disease associated with multiple, large bladder diverticula and present current literature review.

Keywords: Menkes disease; Bladder diverticulum

Introduction
Menkes disease (MD), known also as “kinky hair disease”, Menkes syndrome and “steely hair disease”, is a rare recessive X-linked congenital disorder of copper metabolism with multisystem involvement. The overall incidence of MD is reported to be 1 in 100,000–250,000 births and the vast majority of patients are males. MD occurs due to mutation s in the ATP7A gene, which usually is an intragenic mutation or partial gene deletions. This disease characterized by onset in early infancy shows wide variability in manifestations, ranging from a severe progressive neurodegeneration, connective tissue abnormalities together with peculiar “kinky hair” are the main manifestations. These are caused by deficient or dysfunctional copper absorption and metabolism. Abnormal copper metabolism affects various enzymatic functions, especially lysyl-oxidase activity, which plays a crucial role in collagen and elastin formation [1-4].

The first report of urologic abnormalities associated with Menkes disease was published by Wheeler and Roberts in 1976 [5]. Vesicoureteral reflux (VUR) [5,6,8], hydronephrosis [5,6,8], bladder outflow obstruction [6,7,10], urinary tract infections (UTI) [5,6,7,9], renal rupture [8,10], undescended testes [5,6] and especially large, multiple bladder diverticula [4-13], are often described as part of clinical findings in children with Menkes disease.

The aim of this study is to present two cases of children with Menkes disease associated with multiple, large bladder diverticula as well as a current literature review.

Material and Methods
Over the last five years, two children with Menkes disease underwent urological evaluation in our department/clinic.

Case 1
A four-month-old boy with a typical clinical picture of MD was referred for urological evaluation because of micturition problems. No urinary tract infections were noted (no positive urine cultures). Ultrasound examination (US) showed the presence of three large bladder diverticula, including one with a size equal to the bladder volume (Figure 1 a,b,c). No dilatation of the upper urinary tract was noted. Voiding cystourethrography (VCGU) revealed a huge right-sided bladder diverticulum and two smaller ones located on the left side; massive urine retention within the diverticula was noted after voiding. No vesicoureteric reflux (VUR) was visible (Figure 2 a,b). Because of the progressive neurological deterioration and the generally poor condition as well as the parent’s decision the boy was treated only in a palliative way.

Case 2
A nine-month-old girl with diagnosed MD was referred for urological evaluation because US examination was suggestive of the presence of multiple diverticula. No urinary tract infections or micturition problems were observed. The US showed multiple bladder diverticula with the largest one on the right side; all of them had a wide base communicating with the bladder (Figure 3 a,b,c,d). No dilatation of the upper urinary tract was noted. VCUG showed an extremely large bladder diverticulum and multiple diverticula on the left side (Figure 4 a,b,c). No VUR was noted. Because of the progressive rapid mental retardation and neurological deterioration and based on family preference, further hospital care was decided.

Discussion
Bladder diverticula are classified as primary or congenital and secondary or acquired resulting from infravesical obstruction. Independently of nature, all diverticula are defined as a proptosis of bladder mucosa between defects of the detrusor muscle [14]. A sizeable percentage of children with bladder diverticula will have various congenital syndromes [15].

Congenital bladder diverticula are often found in children with connective tissue or muscle abnormalities, such as prune belly syndrome (PBS), Ehlers-Danlos syndrome, Williams-Beuren syndrome and Menkes disease, including the cutis laxa form [1,13,14].

In most publications, bladder diverticula are noted as the most...
a)

b)
Figure 1 a, b, c: Ultrasound examination of the urinary bladder: Multiple bladder diverticula. The largest is located on the right side (the volume of this diverticulum is comparable to the volume of the bladder).
Figure 2 a, b: Voiding cystourethrography (VCUG): A huge right-sided bladder diverticulum and 2 smaller ones located on the left side; massive urine retention within the diverticula after voiding while bladder is empty; no visible vesicoureteral reflux.
b) [Image]
c) [Image]
frequent urological abnormality associated with MD [4–13]. In a retrospective analysis of the largest published series of 57 children with MD, bladder diverticula were found in 38.6% of patients [10].

The cause of bladder diverticula development in MD is attributed to the decreased lysyl-oxidase activity, which is necessary for the collagen formation [1,4,10,13]. Typically, large as well as multiple diverticula are found in children suffering from MD and they tend to increase in size as the patient grows.

There are no guidelines for the management of bladder diverticula in children. Generally, small and asymptomatic congenital diverticula, which are diagnosed incidentally, are managed conservatively. On the other hand, the diverticula, which are associated with urinary tract infections (UTIs), hematuria, lower abdominal pain, and voiding dysfunction (as a result of the incomplete bladder emptying and/or the bladder outlet obstruction), are usually treated surgically. The spectrum of the operative procedures includes extravesical or intravesical, open or laparoscopic diverticulectomy (with or without ureteral implantation). In cases of acquired bladder diverticula, the first step of the management is to alleviate the intravesical obstruction [14,16–18].

There is no uniform approach and no consensus regarding the treatment of bladder diverticula in patients with Menkes disease. The literature on this topic is sparse and mainly consists of case reports. Some of the reported patients were managed either conservatively (on a best-supportive care basis) or with the implementation of less interventional approaches like clean intermittent catheterizations with or without cutaneous vesicostomy. There are few reports of surgical excision of the diverticula [8,9,12,13]. In all these cases, the presence of clinical symptoms, such as recurrent UTI, incomplete bladder emptying with a massive postvoiding residual volume, was the indication for the operative intervention. In one case the rupture of a large bladder diverticulum required laparotomy and diverticulectomy [8]. The longest described postoperative follow-up is only two years [9]. Finally, no follow-up data regarding bladder function or prevention of UTIs after the resection of the diverticula is available. Both our patients were managed palliatively, because of their clinical status and according to the parents’ informed consent.

Menkes disease is currently considered as a lethal disorder [1]. Because of the poor overall prognosis for these children, the choice of treatment should be based on the clinical condition, the expectations and the decision of the family after its detailed enlightenment [13].
Figure 3 A, B, C, D: Ultrasound examination of the urinary bladder: Multiple bladder diverticula with the largest on the right side; all diverticula have a wide base communicating with the bladder.

Figure 4 A, B, C, D: Ultrasound examination of the urinary bladder:

Figure 4 A, B, C: Voiding cystourethrography (VCUG): An extremely large right-sided bladder diverticulum (the volume of this diverticulum is comparable to the volume of the bladder), a narrow native bladder space and multiple diverticula on the left side are seen.
Conflict of Interest:
The authors declare no conflict of interest.

References

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