Eur J Pediatr (2014) 173:1115–1117
DOI 10.1007/s00431-014-2348-9

CASE REPORT

Aerococcus urinae: a possible reason for malodorous urine in otherwise healthy children

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Received: 22 March 2014 / Revised: 21 May 2014 / Accepted: 23 May 2014 / Published online: 10 June 2014

Abstract Recently, *Aerococcus urinae*, primarily recognized as a common pathogen in elderly women, has been reported to cause an extremely unpleasant odour of the urine in paediatric patients similar to trimethylaminuria (fish odour syndrome). Herein, we present a case of *A. urinae* urinary tract colonization in a 12-year-old otherwise healthy boy, who finally refused micturition outside from his home environment as a result of the unpleasant odour. Within the last year, three cases (including our own) of *A. urinae* colonization causing foul-smelling urine in healthy children have been published, suggesting that this condition might be as frequent as trimethylaminuria. In case of polymicrobial growth in a urine specimen, *A. urinae* as the leading pathogen will usually be missed by routine bacteriological investigation. Novel bacteriological techniques such as MALDI-TOF MS provide a rapid tool to recognize this pathogen in urine. *Conclusion*: As treatment of *A. urinae* infection is simple, we recommend that in healthy children with malodorous urine, this pathogen is excluded before the initiation of costly metabolic investigations.

Keywords *Aerococcus urinae* · Malodorous urine · Paediatrics · MALDI-TOF MS

Communicated by Beat Steinmann

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Abbreviations

A. urinae	*Aerococcus urinae*
FMO3	Flavine-containing monooxigenase-3
MALDI-TOF	Matrix-assisted laser desorption ionization
MS	time of flight mass spectrometry
TMA	Trimethylamine

Case report

A 12-year old healthy boy was referred to our pediatric nephrology outpatient clinic for the assessment of foul smelling urine for several months. He reported that whenever he started to empty his bladder, an extremely unpleasant smell immediately spread in the bathroom and throughout the whole house. As a result of this worrying and embarrassing experience, the boy finally refused micturition outside his home environment. There were no other associated symptoms, in particular, no fever, dysuria, urgency or frequency. His previous medical history was unremarkable. His physical examination was normal, and in particular, he was uncircumcised and without phimosis. Several urine samples examined in private practice were negative for leukocytes and nitrite on dipstick testing. At our clinic, the odour of the two collected clean-catch urine samples was indeed disturbing, reminiscent of furniture polish. After having shortly opened the urine tube, the examination room had to be thoroughly ventilated.

Both samples showed an elevated number of urinary leukocytes (187/μl and 275/μl, respectively, normal range 0–10/μl). Conventional diagnostic microbiology using agar plates for culture and matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS) identified *Aerococcus urinae* (10^6/ml and 10^5/ml, respectively) as the most prominent pathogen in combination with *Corynebacterium species* 10^4 and *Actinomyces neuii* 10^4 in the first and *Corynebacterium simulans* 10^4, *Veillonella* 10^4 and *Bacteriodes fragilis* 10^3 in the second urine sample. Further metabolic investigations including metabolic urine analysis for trimethylaminuria (fish odour syndrome) performed at the metabolic laboratory of the University Hospital in Heidelberg (Germany) showed a normal amount of free trimethylamine (TMA) (10.6 mmol/mol creatinine; normal range 5.7–18.1 mmol/mol creatinine) with a low concentration of total TMA (28.5 mmol/mol creatinine; normal range >100 mmol/mol creatinine).

After a 10 days of antibiotic treatment with amoxicillin/clavulanate, the abnormal urine odour had completely disappeared; the leukocyte count in urine had decreased to 23/μl, and culture had become negative.

Discussion

Current evidence suggests that isolation of *A. urinae* from urine is rare in the pediatric population and mainly found in women above 65 years of age [9]. *A. urinae* usually causes urinary tract infections but has also been described to colonize the urinary tract without infection. Severe infections including septicemia and endocarditis caused by *A. urinae* have also been reported, however, in association with additional risk factors such as diabetes mellitus, neutropenia or other chronic systemic diseases as well as the presence of urinary catheters [9]. In pediatric patients, only three cases of urinary tract infection or colonization with *A. urinae* have been reported so far, and all have been published in the Pediatric Infectious Disease Journal. The first case was reported in 2008 in a 12-year-old boy, who suffered from *A. urinae* pyelonephritis years after having undergone surgery for vesicoureteral reflux [7]. The second case, a 7-year-old healthy boy with foul-smelling urine without symptoms or underlying urological abnormality, reported in 2012, was found to have *A. urinae* bacteriuria (leukocyte count not reported), and after treatment with cotrimoxazole for 7 days, the smell had disappeared as in our case [2]. Finally, in 2013, a third similar case has been published, reporting an 11-year-old boy with no other symptoms than an odd pungent ammoniacal odour of the urine. He received oral penicillin for 3 days after the isolation of *A. urinae* in urine culture [4]. Again, both the bad odour of the urine and the growth of *A. urinae* had disappeared after treatment.

The differential diagnosis of smelly urine is broad: Apart from urinary tract infection or colonization, foods (e.g. asparagus), drugs, metabolic disorders, incontinence and poor hygiene can lead to this symptom. Our patient did not have a urinary tract infection according to international definition criteria [10]. However, mere colonization seemed unlikely as two urinary tract samples collected on separate days grew *A. urinae*, and leucocyte counts were elevated in both samples. Importantly, the cause of the foul odour would have been missed by routine microbiological procedures, as growth of more than one pathogen in a urine sample from an immunocompetent individual is usually considered to represent contamination and therefore not further analyzed or specified. In addition, there is currently no information if *A. urinae* can be detected on dip-slides; therefore, these traditional methods might miss this pathogen. The introduction of MALDI-TOF MS [3, 8] into routine microbiological analysis as done at the microbiological laboratory at the Basel University Hospital, however, enables more detailed analysis of the pathogens including the identification of anaerobic organisms which are not easily cultivable in normal culture media and might also be the reason for a malodorous urine. In a case of a peculiar odour of the urine, most pediatricians initially suspect a metabolic disorder. This usually leads to costly investigations such as metabolic urine analysis to exclude trimethylaminuria (fish odour syndrome) as this rare condition is known to also cause similar foul-smelling urine as the leading symptom. Trimethylaminuria [OMIM: 602079, FMO3, gene locus 1q23-q25] is a rare autosomal recessive disorder. TMA is produced by bacteria in the intestinal tract predominantly from choline (in lecithin e.g. from egg yolk, liver, kidney and beans) or from TMA-N-oxide (from saltwater fish). In the liver, TMA is degraded by flavine-containing monooxigenase-3 (FMO3) to odourless TMA-N-oxide which is excreted in the urine. In primary trimethylaminuria, biallelic loss of function mutations results in decreased enzyme activity and consecutively in an imbalance between the amount of substrate and enzyme capacity. TMA accumulates continuously or intermittently (depending on dietary intake) in body fluids (e.g. urine, sweat) causing the typical fishy odour. Secondary cases of trimethylaminuria may occur in the setting of excess precursor burden such as in the administration of choline for therapeutic purposes. [5, 6]. Urine can be analyzed for the concentration of free and oxidized TMA [11]. The normal concentration of free TMA with a low concentration of total TMA in our patient makes the diagnosis of trimethylaminuria unlikely, although generally a higher level of total TMA is deemed necessary for definitive exclusion of the disease. In addition, the fact that the patient's urine odour rapidly became normal after treatment with amoxicillin makes it even more unlikely that a trimethylaminuria was the underlying cause. Of note, it is well known that many pathogens have the capacity to produce TMA and also other volatile metabolites that could, in principle, explain this symptom of malodorous urine [1].

Prevalence rates of trimethylaminuria are difficult to estimate as the disease is likely underrecognized [5]. The same could be true for foul-smelling urine due to *A. urinae*, given the fact that several similar cases have now been published in a short period of time. In contrast to trimethylaminuria, *A. urinae* colonization or infection can easily be diagnosed, and treatment is simple and effective. Of note and in contrast to the adult population, all cases of *A. urinae* colonization or infection in children have been reported in boys so far. The underlying cause of this gender distribution remains unclear and requires further investigation.

Conclusion

In case of a sudden appearance of malodorous urine in otherwise healthy children, we recommend to first examine the urine for growth of *A. urinae* before initiating costly tests investigating for a metabolic disorder.

Acknowledgments NR is supported by a career advancement grant of the University of Basel. The authors would like to thank Dr. Reno Frei for performing the MALDI-TOF MS in the microbiology laboratory at the Basel University Hospital and for helpful comments on the manuscript. They would also like to thank Dr. Martina Huemer, working as an external metabolic consultant at the University Children's Hospitals of Zurich and Basel, for her support in initiating the metabolic urine analysis and for her helpful comments on the manuscript. Finally, the authors would like to thank Dr. Claus-Dieter Langhans for performing the GCMS analysis at the metabolic laboratory of the Heidelberg University Hospital and for his helpful comments on the manuscript.

Conflict of interest The authors declare that there are no conflicts of interest.

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