COMPANION OR PET ANIMALS

Urate urolithiasis and hyperuricosuria in a Weimaraner, secondary to the SLC2A9 transporter defect

Jodi L. Westropp,1 Eric G. Johnson,2 Mark C. Fuller,2 Noa Safra,3 Danika L. Bannasch3

SUMMARY

In this case, we describe a middle-aged, male Weimaraner that presented with upper and lower urinary tract urate urolithiasis. The dog required surgical intervention to remove the obstruction in the right ureter as well as medical management to prevent recurrent calculi. While the genetic defect that causes this disease in Dalmatians is well known among clinicians, this is the first clinical case documented in the Weimaraner breed. This dog shared the same SLC2A9 mutation as Dalmatians, which likely predisposed this dog to developing urate calculi. For dogs where urate uroliths are suspected on imaging studies, genetic testing may be warranted to help elucidate any predisposing factors for stone formation. Knowing the aetiology of the stone formation will alter the therapeutic approach for treatment and management.

BACKGROUND

Urate-containing calculi have comprised approximately 25 per cent of the calculi analysed at our laboratory each year from dogs (Low and others 2010). Unlike most other breeds of dogs, Dalmatian dogs have a well described alteration in purine metabolism that leads to the excretion of uric acid in the urine rather than excretion of the more soluble metabolite, allantoin (Keeler 1940, Kuster and others 1972). All Dalmatians excrete relatively high amounts of uric acid (400–600 mg of uric acid per day as compared with 10–60 mg/day in non-Dalmatian dogs); however, not all Dalmatians form urate stones (Bartges and others 2005, 2006, Bannasch and others 2008). This genetic abnormality has been described in other breeds (Karmi and others 2010). There is currently a commercial DNA test developed by the Veterinary Genetics Laboratory (http://www.vgl.ucdavis.edu/services/Hyperuricosuria.php) to identify the mutation in the SLC2A9 transporter.

CASE PRESENTATION

A six-year-old male castrated (26 kg (57.2 lbs)) Weimaraner was referred to the William R. Prichard Veterinary Medical Teaching Hospital (VMTH) at the University of California, Davis for possible renal, ureteral and cystic calculi. Two months prior to referral, the dog was presented to the primary care veterinarian for decreased appetite, vomiting and lethargy. On physical examination the dog was febrile (41.1°C (106.0°F)). A urinalysis revealed the presence of pyuria, although a urine culture was not performed. An abdominal ultrasound identified small ureteroliths in the proximal right ureter, and a small splenic nodule. The dog was hospitalised and treated with intravenous fluids (type unknown) and intravenous antimicrobials (ampicillin and enrofloxacin: dosage unknown) and was discharged three days later.

The dog was represented to the primary care veterinarian five weeks later for lethargy and was found to be febrile (40.0°C (104.0°F)). An aerobic urine culture was positive growth of Escherichia coli. A focused abdominal ultrasound was performed by the same veterinarian and identified thickening of the right ureter, continued right ureterolithiasis and a static splenic nodule. These findings were concerning for bacterial ureteritis, pyelonephritis, or combination of the two, and the dog was administered enrofloxacin (approximately 5 mg/kg (2.2 mg/lb), orally, every 24 h) and discharged. Thirteen days later, the dog was re-presented to his primary care veterinarian due to anxiety and vomiting. Additionally, the dog was stranguric and not able to urinate the night prior to presentation, but voided with some difficulty the following morning just prior to examination at the primary care veterinarian. Over the course of the day, the dog’s stranguria progressed and the primary care veterinarian diagnosed a urethral obstruction and admitted the dog to the hospital. A urinary catheter was inserted into the bladder and he was administered enrofloxacin again (approximately 5 mg/kg (2.2 mg/lb), orally, every 24 h) as well as amoxicillin (23 mg/kg (10.4 mg/lb), orally, every 12 h), and was referred to the VMTH the following morning.

Upon presentation to the VMTH, he was bright and alert, but anxious. His vital signs were within normal limits. His rectal temperature was normal at this time at 37.9°C (100.3°F). No significant abnormalities were noted on physical examination. His bladder was palpable, but not enlarged, and penis and prepuce area appeared normal. While in transit to the VMTH, the dog removed the urinary catheter.

INVESTIGATIONS

A complete blood count (CBC) was performed, and all haematologic values were within normal limits. Serum biochemical analyses are reported in Table 1. Only mild abnormalities were present, and...
TABLE 1: Biochemical panel for this Weimaraner at initial presentation to the VMTH and 15 days postcystotomy

<table>
<thead>
<tr>
<th></th>
<th>Initial presentation</th>
<th>15 Days after cystotomy</th>
<th>Reference range</th>
<th>Units</th>
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<tbody>
<tr>
<td>Anion gap</td>
<td>23</td>
<td>14</td>
<td>12–20 mol/l</td>
<td></td>
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<tr>
<td>Sodium</td>
<td>147</td>
<td>146</td>
<td>143–151 mmol/l</td>
<td></td>
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<tr>
<td>Potassium</td>
<td>4.3</td>
<td>4.3</td>
<td>3.6–4.8 mmol/l</td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>110</td>
<td>113</td>
<td>108–116 mmol/l</td>
<td></td>
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<tr>
<td>Bicarbonate</td>
<td>18</td>
<td>23</td>
<td>20–29 mg/dl</td>
<td></td>
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<tr>
<td>Phosphorus</td>
<td>4.9</td>
<td>4.9</td>
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<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>10.7</td>
<td>10.8</td>
<td>9.6–11.2 mg/dl</td>
<td></td>
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<tr>
<td>BUN</td>
<td>12</td>
<td>19</td>
<td>11–33 mg/dl</td>
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</tr>
<tr>
<td>Creatinine</td>
<td>1.0</td>
<td>0.7</td>
<td>0.8–1.5 mg/dl</td>
<td></td>
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<tr>
<td>Glucose</td>
<td>84</td>
<td>83</td>
<td>86–118 mg/dl</td>
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<tr>
<td>Total protein</td>
<td>6.0</td>
<td>5.3</td>
<td>5.4–6.9 g/dl</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.2</td>
<td>2.9</td>
<td>3.4–4.3 g/dl</td>
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<tr>
<td>Globulin</td>
<td>2.8</td>
<td>2.4</td>
<td>1.7–3.1 g/dl</td>
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<tr>
<td>ALT</td>
<td>29</td>
<td>30</td>
<td>21–72 IU/l</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>40</td>
<td>31</td>
<td>20–49 IU/l</td>
<td></td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>284</td>
<td>158</td>
<td>55–257 IU/l</td>
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<tr>
<td>Alkaline phosphatase</td>
<td>156</td>
<td>151</td>
<td>14–91 IU/l</td>
<td></td>
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<tr>
<td>GGT</td>
<td>3</td>
<td>3</td>
<td>0–5 IU/l</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>316</td>
<td>343</td>
<td>139–353 mg/dl</td>
<td></td>
</tr>
<tr>
<td>Bilirubin total</td>
<td>0.1</td>
<td>0.1</td>
<td>0.0–0.2 mg/dl</td>
<td></td>
</tr>
</tbody>
</table>

VMTH, Veterinary Medical Teaching Hospital

all liver function parameters were within the reference ranges. A urine sample was collected by cystocentesis and submitted for urinalysis and urine culture. The urine specific gravity was 1.018 and the urinary pH was 6.0; 25 mg/dl of protein was present. There were 3–5 white blood cells/HPF and 50–100 red blood cells/HPF. No bacteria or crystals were reported, and aerobic urinalysis and urine culture. The urine specimens were sterile.

Due to his anxiety, the dog was sedated with butorphanol (0.2 mg/kg, (0.09 mg/lb), intravenous) and dexmedetomidine (2.5 μg/kg, (1.1 μg/lb), intravenous) for thoracic and abdominal radiographs. Thoracic radiographs were essentially unremarkable. Abdominal radiographs failed to provide definitive evidence of urolithiasis in any portion of the upper or lower urinary tracts.

An abdominal ultrasound was performed. Sonographic findings included clean acoustic shadowing material within the collecting system of the kidneys bilaterally, and multiple regions of clean acoustic shadowing material within the lumen of the right ureter (Fig 1). The right kidney had an irregular capsular margin, blunting of the renal crest, pyelactasia, and hydronephrosis with marked right ureteral wall thickening. The left kidney had similar changes including mild pyelactasia, mild blunting of the renal crest and mild thickening of the left ureter with mild hydronephrosis. No definitive clean acoustic shadowing material was identified in the lumen of the left ureter. Heavy sediment and flat ‘plate-like’ clean acoustic shadowing material was present within the lumen of the urinary bladder (Fig 2). A hypoechoic, well-defined nodule (1 cm × 1 cm) was detected within the splenic parenchyma. These sonographic findings suggested bilateral nephritis and uretersitis with bilateral chronic pyelonephritis. The hard acoustic shadowing material within the collecting system of the kidneys and within the lumen of the right ureter was compatible with bilateral mineralised nephroliths with multiple right ureteroliths. Bilateral hydronephrosis without significant renal diverticular distention suggested bilateral chronic partial ureteral obstruction. Mineralised sediment and debris within the lumen of the urinary bladder was compatible with small cystoliths. The splenic nodule may have represented a benign or malignant change; biopsy was recommended.

Preprandial and postprandial serum bile acids were submitted to rule out an underlying hepatopathy as a cause for suspected urate urolithiasis (see differentials). Both values were within the laboratory’s reference range (preprandial 0 μMOL/l and postprandial 6 μMOL/l; reference interval 0–12 μMOL/l). A buccal mucosa swab DNA sample was submitted for testing at the Veterinary Genetics Laboratory at UC Davis1, and results identified this dog as positive for two copies of the mutation that lead to hyperuricosuria and predisposes dogs to form upper or lower urinary urate urolithiasis.

DIFFERENTIAL DIAGNOSIS

On the basis of history and clinical and diagnostic imaging findings done thus far, our primary differentials included pyelonephritis, ureteral calculi and uroliths resulting in a secondary partial or complete urethral obstruction. Differential diagnoses for urolith composition included calcium oxalate, urate, struvite and cystine; the latter was less likely due to the urinalysis, and because Weimaraners have not been described as a breed predisposed to cystine formation (Low and others 2010). While calcium oxalate and struvite are the most common uroliths submitted to stone analysis laboratories from dogs, these calculi are radiodense. Although struvite uroliths are usually less radiodense than calcium oxalate, they are visible on radiography and often associated with urose-producing bacteria in dogs, such as Staphylococcus species (Osborne and others 1981). Although this dog had a bacterial UTI, most E coli species do not have significant urease producing capabilities. Due to the sonographic evidence of upper and lower urinary tract uroliths which lacked radiopacity, urate uroliths were considered most likely. Primary differentials for the splenic nodule included nodular hyperplasia, haematoma and neoplasia, such as hemangiosarcoma.

TREATMENT

The owner was apprehensive about invasive upper urinary tract surgery at the initial visit, and wished to pursue medical management because the dog was very stable. However, due to concern for recurrent urethral obstruction, we recommended urethrocytostomy followed by a cystotomy if clinically indicated. The dog was anaesthetised and urethrocystoscopy was performed using a flexible urethroscope.2 The urethra was only mildly haemorrhagic, likely secondary to the previous catheterisation. No uroliths were present, however, the bladder was moderately erythematous, and numerous yellow irregular calculi of varying sizes (<1–7 mm) were noted. Following the urethrocytostomy, a laparoscopic-assisted cystotomy was performed, using a 5 mm 30° laparoscope3, where all stones were removed using a combination of grasping and suction (Rawlings and others 2003). The stones were submitted to the G.V Ling Urinary Stone Analysis Laboratory for quantitative analysis

1http://www.vgl.ucdavis.edu/services/Hyperuricosuria.php
2FlexII Uterto Reno Fibroscope, Karl Storz Veterinary Endoscopy, Goleta, CA.
3Karl Storz Veterinary Endoscopy, Goleta, CA.
using polarised light microscopy and infrared spectroscopy, as well as bacterial culture. A section of bladder wall was also collected prior to closure and submitted for aerobic and mycoplasma culture. The surgical site was closed routinely. A splenectomy, or splenic biopsy, was also recommended, but the owner declined. The stone analysis confirmed the uroliths were comprised of 100 per cent ammonium hydrogen urate. Urolith and bladder wall cultures were negative for bacterial growth.

The dog recovered uneventfully and was discharged the following day. Because medical management was elected in an attempt to dissolve the upper tract urate uroliths (Bartges and others 1999), he was discharged with the following diet and medications: Royal Canin U/C (fed to maintain current body condition, but added water to produce frequent urinations) and allopurinol (9.5 mg/kg (4.3 mg/lb), orally, every 12 h). Due to the presumed pyelonephritis, the antimicrobials were also

FIG 1: Sagittal view of the right ureter approximately 5 cm distal to the renal pelvis. There are multiple space-occupying objects within the lumen of the ureter with hyperechoic surface reflections and clean acoustic shadows (white arrows) compatible with ureteral calculi or dense mineralisation

FIG 2: Sagittal view of the urinary bladder with space-occupying objects within the gravity-dependent portion. These objects have a hyperechoic surface and minimal distal acoustic shadowing (white arrows) compatible with cystic calculi
continued at the following dosages: enrofloxacin (9.5 mg/kg (4.3 mg/lb), orally, every 24 h), and amoxicillin (23 mg/kg (10.5 mg/lb), orally, every 12 h). The analgesic, tramadol, was also prescribed as needed (3 mg/kg (1.4 mg/lb) orally, every 8–12 h). The owner reported the dog recovered well and no clinical abnormalities were present four days postsurgery.

The dog was discharged three days after surgery with tramadol as previously prescribed. Acrinormazine was also prescribed to help keep the dog calm (2.2 mg/kg (1 mg/lb), orally, every 8–12 h as needed). The owner returned the dog 16 days later for a scheduled re-evaluation. The owner reported the dog was doing well, consuming only the prescribed diet and had no lower urinary tract signs. He gained 1 kg (2.2 lbs) during the two-week period. The owner had given all prescribed medications as directed, but had discontinued the tramadol because he felt his dog was not exhibiting signs of pain. On physical examination, the dog was bright and alert and no abnormalities were detected. A CBC and serum biochemical panel was evaluated. All values for the CBC were still within the hospital’s reference ranges. Mild changes were again noted in the biochemical panel (Table 1). On urinalysis, the urine specific gravity was 1.012 with 12–18 RBC/HPF and urine pH was 6.0. The remaining sediment was in active and an aerobic urine culture was negative.

To evaluate for changes in the kidney, an abdominal ultrasound was performed. The dog was again sedated with butorphanol (0.2 mg/kg (0.09 mg/lb), intravenous) and dexmedetomidine (2.5 μg/kg (1.1 μg/lb), intravenous) to keep him relaxed during the examination. The mineralised material was still present within the collecting system and renal pelvis of the left kidney, however, pyelactasia and ureteral thickening had resolved. The cortical margin of the left kidney was normal. There was now poor corticomedullary distinction as well as persistent blunting of the renal crest, distention of the renal calyces, and ureteral thickening. Additionally, the previously identified ureteroliths present in the right ureter were static in position. These findings were suggestive of persistent chronic pyelonephritis with chronic partial obstruction of the right ureter with ureteritis. Suture material was identified in the apex of the urinary bladder compatible with recent cystotomy. The splenic mass had not changed in sonographic character.

At this time, surgical intervention was recommended to relieve the obstruction and hopefully preserve renal function. The dog was anaesthetised, and a right ureterotomy was performed through a ventral midline laparotomy. A single ureterocele was also excised. No further ureteroliths were observed. The abdomen was closed in routine fashion, and the dog recovered from anaesthesia without complication.

OUTCOME AND FOLLOW-UP
The dog was discharged three days after surgery with tramadol as previously prescribed. Acropromazine was also prescribed to help keep the dog calm (2.2 mg/kg (1 mg/lb), orally, every 8–12 h as needed). The owner returned the dog 16 days later for a scheduled re-evaluation. The owner reported the dog recovered well from surgery. The dog continued to consume the previously prescribed diet. Allopurinol was also continued at the previously prescribed dosage. His physical examination was essentially unremarkable. The abdominal incision healed well and the sutures were removed. A urine culture was repeated because the dog was not receiving antimicrobials, and the culture was negative for growth. On abdominal ultrasound, the left kidney remained static in appearance. Mineralisation was persistent in the collecting system of the right kidney, but the degree of renal pelvic and ureteral dilation had improved. No sonographic evidence of ureterolithiasis was identified in the urinary tract. Mild sediment was present in the bladder.

The dosage of allopurinol was decreased to a ‘prevention dose’ (6 mg/kg (2.7 mg/lb), orally, every 12 h) (Plumb 2011), and the owner was instructed to continue feeding the Royal Canin U/C diet with added water. The dog continued to do well and was seen for a scheduled re-evaluation four months later. The owner did not report any problems with the dog. He was sedated with dexmedetomidine (4 μg/kg (1.8 μg/lb), intravenous) and butorphanol (0.2 mg/kg (0.09 mg/lb), intravenous) for an abdominal ultrasonographic examination. A low-density concretion, which lacked distal acoustic shadow, was identified within the urinary bladder. This may have represented an aggregate of sediment or a low-density cystic calculus, presumably urate, however, xanthine was also considered due to allopurinol administration to the dog (Ling and others 1991). Chronic right kidney changes were present which were likely secondary to the historic pyelonephritis. Mineralisation within the collecting systems of both kidneys was still present but to a lesser degree when compared with previous examinations. Persistent, but improving right ureteral thickening was also noted.

The owner was reluctant to proceed with further surgery, and returned 15 days later to have the ultrasound performed again. No sedation was used for this examination, and a brief ultrasonographic evaluation of the urinary bladder was performed with the patient standing. A rounded, hyperchoic structure with a partial distal acoustic shadow was present along the cranioventral bladder wall. A cystoscopy was again performed, but the stone was too large to be removed safely from the urinary bladder via basket retrieval. The owner declined laser lithotripsy and a cystotomy was performed as previously described. The dog recovered well and was discharged. The stone analysis revealed the stone was comprised of 100 per cent ammonium hydrogen urate. Therefore, the dosage of allopurinol was increased to the previously administered dose. The dog has not had recurrence of uroliths at the time of this writing.

DISCUSSION
In this case report, we describe a Weimaraner presenting with clinical urate urolithiasis that we were able to document had two copies of the hyperuricosuria mutation, which likely predisposed him to developing urate uroliths. In addition to the Dalmatian breed, other breeds such as the English bulldog and the black Russian terrier have been reported to also be homozygous for the same mutation (Karmi and others 2010). Furthermore, the hyperuricosuria mutation has been identified in a number of unrelated dog breeds. Mutant allele frequencies that range from 0.26–25.41 were identified in the American Staffordshire terrier, Australian shepherd, German shepherd dog, giant schnauzer, parson (Jack) Russell terrier, labrador retriever, large Munsterlander, pomeranian, South African Boerboel, as well as the Weimaraner breed (Karmi and others 2010). Notably, the mutation frequency within the Weimaraner breed is as high as the frequency within the English bulldog, approximately 25 per cent. While this mutation has been documented in these breeds, clinicians rarely report clinical urate urolithiasis in most of them. To our knowledge, this is the first reported case of a Weimaraner with clinical urate urolithiasis and documented genetic predisposition for it. Of the 11 other Weimaraners or Weimaraner crosses identified in our stone laboratory database, only one dog had a urolith, which was comprised of only 20 per cent ureter in the core of one stone. All other
Ureteroliths were comprised of struvite (Westropp, unpublished data). A larger number of Weimaraners would need to be assessed to know how prevalent the clinical disease is within the breed.

Because ureteral obstructions have been described in dogs with hepato-pathies and congenital portosystemic shunts, serum bile acids as well as an abdominal ultrasound were evaluated. Both tests failed to provide evidence of hepatic dysfunction. We felt these diagnostics were warranted for several reasons including the mild changes in serum alkaline phosphatase (ALP) and slightly decreased glucose and albumin. Because the serum bile acids were within the reference range, we felt these abnormalities were mild and not clinically relevant to his current condition and should be monitored. The mild hypoglycaemia was likely due to delayed laboratory processing, and the ALP decreased on subsequent re-evaluations. Serum bile acids are an inexpensive, non-invasive, sensitive diagnostic test to screen for portosystemic shunts (Bridger and others 2008) and should be considered in breeds where ureterolithiasis is not commonly described. Genetic testing results returned five days after the dog’s first visit and confirmed our suspicion that the ureterolithiasis was likely secondary to a heritable defect.

It is important for clinicians to have knowledge of breeds with heritable genetic disorders. This allows for client education on underlying causes, help with breeding plans, and dictates further diagnostics. The mutant allele frequencies vary among breeds and can be used to determine an appropriate breeding plan for each breed. If concerned about ureteral obstruction, a DNA test is available for dogs and may be used by breeders to decrease the mutant allele frequency in breeds that carry the mutation. Additionally, veterinarians may use the test as a diagnostic tool to identify predisposing factors for ureteral obstruction, which may alter management strategies used. For example, allopurinol can be considered in dogs with the genetic mutation, but it should not be administered to (or used with extreme caution in) dogs with hepatic disease, and does not appear effective at dissolving ureteroliths in dogs with portovenous anomalies (Plumb 2011).

While there are some case reports to suggest ureteroliths can be dissolved with the xanthine oxidase inhibitor and low purine diet, (Bartges and others 1999) we were unsuccessful in this case. This was not too surprising, as it has also been reported that complete dissolution of ureteroliths occurred in only 36 per cent of 25 Dalmatian dogs using a similar protocol (Adams and Syme 2005). The owner was very reluctant to pursue aggressive upper urinary tract surgery initially and, therefore, due to the positive genetic test, a medical treatment protocol was implemented so long as the dog was monitored closely. It is possible the obstruction could have progressed further and loss of renal function was a risk with this protocol. Upon re-examination, evidence of renal obstruction was progressive and surgery was recommended. A ureterotomy was performed to remove the large ureolith, although why it appeared as multiple ureteroliths sonographically is not well understood. The noted findings may have been mineralised debris present in the ureter, or the single calculus was shaped like an aggregate of stones. In light of the normal postureterotomy contrast pyelo-ureterogram, we elected to not place a ureteral stent. If this dog develops additional ureteroliths or the ureteral obstruction recurs, a ureteral stent can be considered at that time.

The dosage of the allopurinol was decreased after his surgery because we have found in our experience that dogs with the genetic mutation can be managed well using only dietary therapy.\textsuperscript{vii} Side effects of allopurinol include hepatotoxicity and xanthine stone formation (Ling and others 1991). The analysis of the second ureolith confirmed it was comprised of ammonium urate, therefore, the dosage of allopurinol was increased. Allopurinol metabolism varies among dogs (Ling and others 1997), and this Weimaraner may continue to require the higher end of the dosage, and the dog will continue to be monitored.

Contributors

JLW: primary clinician overseeing case; wrote and edited manuscript.
EGJ: boarded radiologist who performed all imaging studies and assessments, wrote and edited manuscript.
MCF: primary surgeon involved with the case; wrote and edited manuscript.
NS and DBL: Performed and interpreted genetic testing; wrote and edited manuscript.

Competing interests

None.

Patient consent

Obtained.

Provenance and peer review

Not commissioned; externally peer reviewed.

REFERENCES


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