Table 2. Concordance between agitated saline bubble—enhanced ultrasound and chest radiography for identifying appropriate hemodialysis catheter tip positioning

|                      | Chest x-ray+ | Chest x-ray− |
|----------------------|--------------|--------------|
| Agitated saline bubble—enhanced ultrasound | 82           | 0            |
| Agitated saline bubble—enhanced ultrasound | 2           | 7            |

**Concordance between agitated saline bubble—enhanced ultrasound and chest radiography.**

| Sensitivity ($\text{aSensitivity} = \frac{\text{true positive}}{\text{true positive} + \text{false negative}}$) | Specificity ($\text{Specificity} = \frac{\text{true negative}}{\text{true negative} + \text{false positive}}$) | Diagnostic accuracy ($\text{Diagnostic accuracy} = \frac{\text{true positive} + \text{true negative}}{\text{true positive} + \text{false negative} + \text{true negative} + \text{false positive}}$) |
|-------------------------------------------------|---------------------------------|-------------------------------------------------|
| 98%                                             | 100%                            | 98%                                             |

True positive result denotes correct placement of hemodialysis catheter according to bubble-enhanced ultrasound and chest radiography. True negative result = incorrect placement of hemodialysis catheter according to bubble-enhanced ultrasound and chest radiography. False positive result = correct placement of hemodialysis catheter according to bubble-enhanced ultrasound not confirmed by chest radiography. False negative result = incorrect placement of hemodialysis catheter according to bubble-enhanced ultrasound not confirmed by chest radiography.

In conclusion, the dynamic ultrasound visualization of microbubbles in the right atrium was highly accurate to identify adequate placement of hemodialysis central venous catheters and significantly faster than bedside chest radiography. It allowed the immediate start of renal replacement therapy, thereby expediting patient care.

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Received 2 March 2017; accepted 31 March 2017; published online 7 April 2017

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**DISCLOSURE**

All the authors declared no competing interests.

**RESEARCH LETTERS**

Renal Involvement in Methylmalonic Aciduria

To the Editor: Isolated methylmalonic acidemia/aciduric aciduria (MMA) is a rare metabolic disorder caused by complete or partial deficiency of the enzyme methylmalonyl-CoA mutase (mut$^0$ or mut$^-$ enzymatic subtype, respectively), a defect in the synthesis or transport of its cofactor, adenosyl-cobalamin (cblA, cblB, or cblD-MMA), or deficiency of the enzyme methylmalonyl-CoA epimerase. The clinical spectrum...
of isolated MMA ranges from the classic neonatal type, infantile, intermediate to the atypical adulthood type.6 All these phenotypes are characterized by periods of relative health and intermittent metabolic decompensation, usually associated with infections and stressful events. MMA can be associated with many complications including cognitive impairment, renal failure, and metabolic stroke affecting the basal ganglia and leading to disabling movement disorders with choreaathetosis, dystonia, and para/quadriaparesis. Other systemic complications include pancreatitis, cardiomyopathy, growth retardation, functional immune impairment, and optic nerve atrophy.7 Renal manifestations of MMA have not been well described. The aim of this study was to report the renal manifestations of MMA in a cohort of patients with MMA in the eastern region of Saudi Arabia.

**METHODS**

This was a single-center, retrospective evaluation of a cohort of patients with MMA who were diagnosed with MMA and followed up at Johns Hopkins Aramco Healthcare (JHAH) between 1984 and 2016. The computer database of JHAH was used to extract patients’ information. MMA was suspected based on the presence of the typical clinical and biochemical manifestations (acute encephalopathy, metabolic acidosis, hyperammonemia, and ketosis) or a history of a previously affected family member. Gas chromatography–mass spectrometry of the urine was used to screen for increased excretion of methylmalonic acid and presence of methyl citrate (typically seen in MMA) in all patients suspected of having MMA, in conjunction with other biochemical profiles including plasma amino acids, acylcarnitines, and serum carnitines. A mutase enzyme activity and vitamin B12 complementation study in cultured skin fibroblasts was conducted to confirm the diagnosis in all patients. A genetic study of MMAB, and mut genes was performed in at least 1 affected family member in 4 of the reported families to identify the family genotype. All the basic biochemical studies were done at the Mayo Clinic biochemical laboratory (Rochester, MN). The enzyme and complementation study was performed either at the department of human genetics at Yale University (New Haven, CT) or at the laboratory of Dr. D. Rosenblatt at McGill University Health Center (Montreal, QC, Canada).

Renal function was assessed by measuring serum creatinine and estimated glomerular filtration rate (eGFR) using the bedside Schwartz formula.7 In addition, patients were evaluated for the presence of electrolyte abnormalities, proteinuria, hematuria, and acidification defect. Acidification defect was defined as a urinary pH ≥ 6.0 in the presence of metabolic acidosis with a blood gas pH ≤ 7.30. Patient survival was calculated using Kaplan–Meier method. Numerical data were expressed as mean or median plus or minus SD. Correlation between serum methyl malonic acid (MA), urinary MA, and eGFR was made by using the Pearson correlation test. Data were expressed together with the 95% confidence intervals and P values. A P value of < 0.05 was considered significant.

The study was approved by the institutional review board at Johns Hopkins Aramco Healthcare.

**RESULTS**

In all, 11 patients from 5 families were identified during the study period. All patients received their medical care from a biochemical geneticist, nephrologist, and/or pediatrician with a special interest in biochemical diseases, with a close monitoring of their growth, development, and biochemical profiles. They were all treated with a protein-restricted diet supplemented with a modified special formula and L-carnitine. Two patients required gastrostomy tube feeding at a certain period of their life.

Of the patients, 4 were female and 7 were male (Table 1). All were of Saudi Arab origin except 1 patient from family 4 who was Saudi/Lebanese. The median age of diagnosis of MMA was 7 ± 102 days (range, 1–270 days).

Three families originated from an isolated geographic area (families 1, 2, and 3 were from an eastern region of Saudi Arabia). All had the same

| Family | Patient | Gender | Age at diagnosis | Age at death | Biochemical defect | Genotype |
|-------|---------|--------|------------------|--------------|-------------------|----------|
| 1 S   | FS      | F      | 1 wk             | 6 mo         | Cobalamin B       | Homozygous c.557G>A(p.R186Q) |
|      | AS      | M      | 9 mo             | Alive 27 yr  |                   |          |
|      | HS      | M      | 1 d              | Alive 16 yr  |                   |          |
|      | MS      | M      | 4 d              | Alive 12 yr  |                   |          |
| 2 E   | ME      | M      | 1 d              | 4 yr         | Cobalamin B       | Homozygous IVS2-10G>T |
|      | AE      | M      | 3 d              | 14 yr        |                   |          |
|      | ME2     | M      | 3 d              | Alive 18 yr  |                   |          |
|      | HE      | F      | 9 mo             | 21 yr        |                   |          |
| 3 M   | FM      | F      | 3 mo             | Alive 20 yr  | Cobalamin B       | Compound heterozygous IVS2-1 G>T;c.557G>A(p.E193K) |
| 4 D   | RD      | M      | 1 wk             | Alive 22 yr  | Mutase<sup>0</sup> | Homozygous c.1871A>G(p.Q624R) |
| 5 D2  | SD      | F      | 1 wk             | 14 yr        | Mutase<sup>0</sup> | Not done |

F, female; M, male.
biochemical defect (Cobalamin B), but different genotypes. Patients with the Cobalamin B defect had a less severe phenotype and displayed good response to vitamin B12 therapy. One patient from family 3 with a compound heterozygous displayed the milder phenotype of all the described patients. However, she showed no response to vitamin B12 therapy. One patient died early at the age of 6 months due to severe metabolic decompensation. One patient developed end-stage renal disease at the age of 27 years and died before initiation of renal replacement therapy.

The other 2 families had the typical mutase0 deficiency and had a more severe phenotype. One of the 2 patients with mutase0 deficiency (family 4) underwent a combined liver/kidney transplantation at the age of 14 years and is doing well 8 years after transplantation, with normal liver and renal graft function. The other patient (from family 5) died at the age of 14 years.

The mean eGFR was 71 ± 20 ml/min/1.73 m² body surface area (range, 43–94 ml/min/1.73 m² body surface area) at the age of 3 years (Table 2). Manifestations of renal dysfunction such as electrolyte abnormalities and acidification defects are listed in Table 3. Persistent hyperkalemia was not found in any patient, although hyperkalemia during metabolic decompensation was common and was found in 70% of patients. Persistent hypokalemia was found in 30% of patients. Overt proteinuria was not found in any patient, even those with advanced renal failure.

There was no correlation between eGFR at age 3 years and either urinary MA excretion or serum MA level, nor was there a correlation between serum MA level and urinary excretion of MA (Table 4).

Renal biopsy was performed in 1 patient from family 3 with a compound heterozygous genotype at age 14 years. The results showed extensive chronic changes involving all components of the parenchyma, including focal global glomerulosclerosis and moderately extensive tubular atrophy and interstitial fibrosis. The mesangium was unremarkable. There was moderate interstitial inflammation with evidence of tubulitis. Immunofluorescence histology showed no positive staining. Ultrastructural examination showed relatively well preserved foot processes of the visceral epithelial cells. The glomerular basement membranes were normal. No electron-dense deposits were identified, and the endothelial cells were unremarkable.

Most patients lived into adulthood, with a median survival of 22 years (Figure 1).

### Table 2. Urinary methylmalonic acid (MA), serum MA, and estimated glomerular filtration rate (eGFR) at the age of 3 years

| Patient | eGFR ml/min/1.73 m² | Urinary MA µg/mg Cr (< 3.59) | Serum MA nmol/ml (< 0.4) |
|---------|---------------------|-----------------------------|--------------------------|
| HS      | 94                  | 7054                        | 671                      |
| MS      | 92                  | 22384                       | 354                      |
| AS      | 90                  | 3430                        | 1080                     |
| ME      | 76                  | ?                            | 456                      |
| AE      | 43                  | 10538                       | 926                      |
| ME2     | 78                  | 7914                        | 1670                     |
| HE      | 56                  | 5246                        | 355                      |
| FM      | 44                  | 13450                       | 728                      |
| RD      | 59                  | 4836                        | 1890                     |
| SD      | 75                  | 4220                        | 536                      |

### DISCUSSION

Isolated MMA is one of the organic acidurias that is rare and associated with substantial morbidity and mortality with many complications, including growth retardation and visceral and neurological impairment. Most cases are diagnosed based on clinical presentation. However, molecular genetic testing is required to make a more definitive diagnosis. Expanded neonatal screening using tandem mass spectrometry has been shown to decrease early mortality, with less severe symptoms at diagnosis and more favorable short-term neurodevelopmental outcomes. Most individuals with isolated MMA develop renal insufficiency, even those who are mildly affected. Chronic kidney disease is more commonly associated with vitamin B12–nonresponsive forms of MMA and in individuals with the mut0 enzymatic subtype (61%) and the cblB enzymatic subtype (66%), and occurs less frequently in those with the cblA enzymatic subtype (21%).

The pathogenesis of renal injury associated with MMA is not clear. Increased ammonia genesis in the proximal tubule in the setting of metabolic acidosis has been implicated as a possible mechanism that leads to worsening renal function. Nath et al. observed, in a rat model, that nitrogen nucleophiles such as ammonia are injurious to the kidney and stimulate chronic tubulo-interstitial inflammation through activation of the alternative complement pathway. Involvement of dicarboxylic acid transport has also been hypothesized as a possible mechanism of renal injury in patients with MMA. In a mouse model, the primary pathological manifestation of kidney injury in MMA was believed to be mediated through mitochondrial dysfunction in the

### Table 3. Renal abnormalities in patients with methylmalonic acidemia/aciduria

| Persistent hyperkalemia | Hyperkalemia during decompensation | Hypokalemia | Proteinuria | Hematuria | Urinary acidification defect |
|-------------------------|------------------------------------|-------------|-------------|-----------|----------------------------|
| 0                       | 7 (70)                             | 3 (30)      | 0           | 1 (10)    | 2 (20)                     |

Data are number of patients (%).
correlated with serum creatinine. Serum creatinine has been previously observed when GFR was measured and occurs at an early age in patients with MMA, and that has stage renal disease. We believe that renal impairment reaches that of adults by the end of the second year of life. Most of our patients with MMA had renal impairment by the age of 3 years, and a few progressed to end-stage renal disease. We believe that renal impairment occurs at an early age in patients with MMA, and that has been previously observed when GFR was measured and correlated with serum creatinine. Serum creatinine as a surrogate marker of renal function may be misleading, as it likely overestimates the true GFR as a result of decreased muscle mass in patients with MMA who are protein malnourished. Other markers of renal function may be more reflective of GFR, such as cystatin C.

Renal tubular acidosis is expected in patients with MMA, considering the severity of tubulo-interstitial nephritis as demonstrated in the kidney biopsy. However, the majority of our patients were able to lower the urinary PH even during metabolic decompensation. This was observed even in patients with advanced renal failure. The low urine PH in the setting of hyperchloremic metabolic acidosis observed in patients with MMA suggests either proximal, type 2 or distal, type 4 rather than the distal, type 1 renal tubular acidosis. Urinary acidification defect has been previously reported in case reports and small series. In a series of 7 patients with MMA, urinary acidification defect was found in only 2 patients, although several patients had hyporeninemic hypoaldosteronism suggesting type 4 renal tubular acidosis. Excretion of large quantities of MA in the urine during episodes of metabolic decompensation may also contribute to the low urinary PH.

Hyperkalemia is not a common feature of MMA and has been reported in case reports. Among our patients, hyperkalemia was observed only during metabolic decompensation and usually corrected once the metabolic crisis had resolved.

Overt proteinuria was not found in any patient, even in those with advanced renal failure, reflecting the nature of the underlying pathology with mainly tubulo-interstitial rather than glomerular involvement. This was confirmed by ultrastructural examination of the renal biopsy sample, which showed relatively well-preserved foot processes of the visceral epithelial cells. Our study has several limitations, related mainly to the retrospective nature of the study. In addition, and because of the rarity of MMA, the number of patients included is small. However, this is one of the largest series ever published in patients with MMA. We also used serum creatinine for estimation of GFR rather than more precise measures such as inulin or iohalamate clearance.

In summary, the majority of patients with MMA develop renal impairment at a young age. Most patients are able to acidify the urine, have no overt proteinuria, and have no significant electrolyte abnormalities. With proper medical care, most patients can survive into adulthood. Liver transplantation is curative, and patients with advanced renal failure may benefit from combined liver and kidney transplantation.

**Table 4.** Correlation between estimated glomerular filtration rate (eGFR) at age 3 years, and urinary and serum methyl malonic acid (MA)

| Correlates                  | r    | 95% Cl       | P value |
|-----------------------------|------|--------------|---------|
| eGFR versus urinary MA      | 0.142| –21.7 to 30.1| 0.71    |
| eGFR versus serum MA        | –0.110| –0.26 to 20.60| 0.78    |
| Urinary versus serum MA     | –0.557| –14.4 to 2.04| 0.12    |

CI, confidence interval; r, Pearson correlation coefficient.

The authors acknowledge the use of Johns Hopkins Aramco Healthcare (JHAH) facilities for research data used in this article. Opinions expressed in this article are those of the authors and not necessarily of JHAH.
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Received 25 February 2017; revised 11 April 2017; accepted 14 April 2017; published online 28 April 2017

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Kidney Int Rep (2017) 2, 956–960; http://dx.doi.org/10.1016/j.ekir.2017.04.007

The Effect of War on Syrian Refugees With End-Stage Renal Disease

To the Editor: The number of refugees in the world exceeds 20 million, with Syrians constituting close to a quarter of them, including about 629,000 in Jordan in 2015. Health care coverage of refugees varies by host country, but the United Nations High Commissioner for Refugees is the major payer. The United Nations High Commissioner for Refugees does not cover the expenses of many chronic diseases including end-stage renal disease (ESRD). Studies from the Syrian War and other wars showed a major negative impact on the expenses of many chronic diseases including end-stage renal disease (ESRD). Studies from the Syrian War and other wars showed a major negative impact on the