Uremic Thrombocytopathy Is not about Urea

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ABSTRACT

Platelet dysfunction in renal failure is attributable to high levels of small, partly dialyzable molecules known as uremic toxins, hence the term “uremic thrombocytopathy.” Although a variety of moieties contribute to platelet dysfunction or abnormal interactions between platelets and the vascular wall, urea remains a potential factor. Here, we studied three family members with familial azotemia, a rare autosomal dominant syndrome characterized by high plasma urea resulting from impaired urinary excretion but normal renal function otherwise. Platelet function, assessed in vitro and by traditional bleeding time, was normal in all individuals. Abnormal platelet function in patients with renal failure is not caused by high concentrations of urea.


Platelet dysfunction is often seen in patients with advanced renal disease, and urea is considered one of the responsible metabolites.1,2 Consequently, uremic thrombocytopathy is commonly used to describe this disorder. The exact contribution of urea toward platelet dysfunction as opposed to other metabolites in uremic plasma is difficult to assess, because both arise at the same time in such individuals.

Three patients with rare familial azotemia (OMIM #109160) allowed us to evaluate platelet function in the setting of isolated high plasma levels of urea. Familial azotemia was first described as an autosomal dominant disorder in 1978,3 and only one other case has been described since.4 Patients with familial azotemia have isolated high levels of urea as a result of as-yet-unexplained defects in urea excretion. Despite the high urea level, affected individuals have otherwise normal renal function and seemingly good health.

Both adult patients (the index case and her brother) in our study were known to have high levels of urea with normal serum creatinine levels since childhood. Although a pediatric nephrologist saw them occasionally, no definitive diagnosis was made at that time. Renal function studies performed at the age of 3 years in the index case demonstrated normal kidney function (GFR 74 ml/min per 1.73 m² with an estimated renal plasma flow of 379 ml/min) with suboptimal urine-concentrating ability (607 mOsm/L after administration of desmopressin). Her urea excretion, however, was exceptionally low (1.1 ml/min). Ultimately, because of short stature, it was decided to impose a protein-restricted diet and, despite that diet, she continued to grow.

Both patients were lost to follow-up until the index case, at age of 29, had a child with the same biochemical abnormalities. Both the index case and her similarly affected brother and their parents and the newborn were reexamined. The index case and her brother did not have any symptoms of uremia; in particular, they experienced no nausea, itching, or spontaneous bleeding. Physical examination at the time of this study demonstrated two adults in good health apart from being short (approximately 150 cm). BPs were normal, as were levels of hemoglobin (Table 1). Blood urea levels were high with severely reduced urea clearance (approximately 5 ml/min) in the index case and her brother and the newborn. All members of our pedigree had normal creatinine clearances, and a diagnosis of familial azotemia was made. We assume our pedigree behaves in an autosomal dominant manner. Although both parents of the index case have normal levels of blood urea, the mother of the index case has a reduced urea clearance and presumably is a carrier with incomplete penetrance or mosaic.

Bleeding times in the two affected adults (and their mother) were normal (Table 1). An automated platelet function analyzer showed normal clotting times in response to ADP and epinephrine in the index case and to epinephrine in her child. In addition, aggregation tests in response to arachidonic acid and collagen were irreversible in the child, which is also consistent with normal platelet function (data not shown).

To date, the underlying molecular defect in familial azotemia is unclear. Several urea transporters (UT) are known to play a role in urea clearance (UT-A, UT-B), but...
null mouse models of these transporters do not express high levels of urea. Thus, a deficiency of these transporters in the described adults seems unlikely.

Familial azotemia is a unique genetic human variant to study the effects of high urea levels in the absence of other toxic metabolites seen in renal failure. Uremic thrombocytopenia is caused by impaired platelet function or platelet wall abnormalities in patients with severe renal insufficiency, although the exact toxic effect of the aforementioned metabolites were seen in the three patients described here, who have had chronic high levels of urea with otherwise normal renal function.

Several factors are implicated in the occurrence of platelet dysfunction in patients with renal failure. These could be platelet derived, vessel wall derived, or caused by other factors. There is conflicting evidence on why platelet abnormalities are found in renal failure, but increases in cAMP and decreases in thromboxane A2 formation are reported regularly. Increased synthesis of prostacyclin, an inhibitor of platelet function, or a quantitative or qualitative defect in von Willebrand factor attributed to altered vascular endothelium and may also influence platelet function. Finally, a low hematocrit, leading to impaired platelet adhesion to the vessel wall, and high levels of nitric oxide, a potent inhibitor of platelet function, may also contribute to platelet dysfunction.

The aforementioned metabolites were not measured in our patients, but their normal creatinine clearance and physical examination do not suggest there would be other accumulated toxins. We conclude that high levels of urea do not influence platelet function, as shown in our patients with familial azotemia, but cannot rule out the possibility that high levels of urea are necessary to activate other toxic metabolites in the setting of renal failure.

### CONCISE METHODS

#### Patients
Patients were examined as part of routine patient care, and blood and urine were obtained from family members with informed consent and institutional review board waiver (09.17.1891). Assessment of bleeding time was done because renal biopsy was considered for all family members.

#### In Vitro Platelet Function
For studying in vitro platelet function, a butterfly needle was inserted into the cubital vein without the use of a tourniquet. The first two samples were discarded, after which a sample was drawn for platelet function analyses. Whole blood was anticoagulated with 3.2% sodium citrate (1:9 vol:vol). Platelet-rich plasma (PRP) was prepared by centrifugation at 2000 × g for 15 minutes for the difference in light transmission between platelet-poor plasma and PRP. Platelets were activated by addition of ADP (Bio Data Corp., Horsham, PA) at a concentration of 5 μmol/L, arachidonic acid (Bio Data Corp.) at a concentration of 2 mmol/L, ristocetin (Trinity Biotech Company Bray, Wicklow, Ireland) at a concentration of 1.25 g/L, and collagen type I (Chrono-Par; Chrono-log Corp.) at a concentration of 1.0 mg/L. In addition, analyses using a Platelet Function Analyzer (Siemens, Newark, NJ) were performed using Collagen/Epinephrine and Collagen/ADP cartridges obtained from the manufacturer.

#### In Vivo Platelet Function
In vivo platelet function was studied by traditional Ivy bleeding time. In short, an incision of standardized length and depth was made into the subpapillary plexus of the forearm skin using a Surgicutt (ITC Medical) device. Capillary pressure was constantly increased by applying a BP cuff, inflated to 40 mmHg, on the upper arm. Subsequently, blood emerging from the incision was removed with a piece of filter paper until oozing of blood had stopped. The time (in minutes) between the incision and cessation of oozing was recorded as the bleeding time.

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DISCLOSURES
None.

REFERENCES