

inappropriately high compared with plasma osmolality, but vasopressin levels are below the limits of RIA detection in a certain portion of the patients (as much as 10 to 20%).¹² The existence of other antidiuretic substances in plasma has been postulated. Oxytocin may fit this profile nicely. A few studies have shown elevated levels of plasma oxytocin in patients with small-cell lung cancer; however, these increments were usually accompanied by concomitant increases in vasopressin.¹³ At present, no report has suggested that oxytocin alone produces SIADH in clinical cases, but this may be attributable to the lack of a reliable RIA for oxytocin in clinical settings. Related to this topic, the nephrogenic syndrome of inappropriate antidiuresis (NSIAD) is caused by a gain-of-function mutation of V2R. In this disease, endogenous vasopressin is completely suppressed while antidiuresis persists.¹⁴ The symptoms of disease start from childhood, but similar mutations seem to explain some sporadic episodes of SIADH in adults.¹⁵

How should we differentiate oxytocin-induced SIADH from NSIAD? Oxytocin-induced SIADH will respond to V2R antagonists as illustrated by *Li et al.*¹⁰, whereas patients with NSIAD are unable to respond to V2R antagonists.¹⁵ Clinicians would thus be well advised to note that oxytocin has antidiuretic activity and contributes to hyponatremia in certain clinical settings and that V2R antagonists may be useful in the differential diagnosis and treatment of inappropriate antidiuresis.

DISCLOSURES

None.

REFERENCES

- Sausville E, Carney D, Battey J: The human vasopressin gene is linked to the oxytocin gene and is selectively expressed in a cultured lung cancer cell line. *J Biol Chem* 260: 10236–10241, 1985
- Chini B, Manning M: Agonist selectivity in the oxytocin/vasopressin receptor family: New insights and challenges. *Biochem Soc Trans* 35: 737–741, 2007
- Birnbaumer M, Seibold A, Gilbert S, Ishido M, Barberis C, Antaramian A, Brabet P, Rosenthal W: Molecular cloning of the receptor for human antidiuretic hormone. *Nature* 357: 333–335, 1992
- Fushimi K, Uchida S, Hara Y, Hirata Y, Marumo F, Sasaki S: Cloning and expression of apical membrane water channel of rat kidney collecting tubule. *Nature* 361: 549–552, 1993
- Ishikawa SE, Schrier RW: Pathophysiological roles of arginine vasopressin and aquaporin-2 in impaired water excretion. *Clin Endocrinol* 58: 1–17, 2003
- Sasaki S, Noda Y: Aquaporin-2 protein dynamics within the cell. *Curr Opin Nephrol Hypertens* 16: 348–352, 2007
- Pittman JG: Water intoxication due to oxytocin. *N Engl J Med* 268: 481–482, 1963
- Potter RR: Water retention due to oxytocin. *Obstet Gynecol* 23: 699–702, 1964
- Chou CL, DiGiovanni SR, Mejia R, Nielsen S, Knepper MA: Oxytocin as an antidiuretic hormone. I. Concentration dependence of action. *Am J Physiol* 269: F70–F77, 1995
- Li C, Wang W, Summer SN, Westfall TD, Brooks DP, Falk S, Schrier RW: Molecular mechanisms of antidiuretic effect of oxytocin. *J Am Soc Nephrol* 19: 225–232, 2008
- Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH: Hyponatremia treatment guideline 2007: Expert panel recommendations. *Am J Med* 120: S1–S21, 2007
- Robertson GL: Regulation of arginine vasopressin in the syndrome of inappropriate antidiuresis. *Am J Med* 119: S36–S42, 2006
- North WG, Friedmann AS, Yu X: Tumor biogenesis of vasopressin and oxytocin. *Ann N Y Acad Sci* 689: 107–121, 1993
- Feldman BJ, Rosenthal SM, Vargas GA, Fenwick RG, Huang EA, Matsuda-Abedini M, Lustig RH, Mathias RS, Portale AA, Miller WL, Gitelman SE: Nephrogenic syndrome of inappropriate antidiuresis. *N Engl J Med* 352: 1884–1890, 2005
- Decaux G, Vanderghyest F, Bouko Y, Parma J, Vassart G, Vilain C: Nephrogenic syndrome of inappropriate antidiuresis in adults: High phenotypic variability in men and women from a large pedigree. *J Am Soc Nephrol* 18: 606–612, 2007

See related article, "Molecular Mechanisms of Antidiuretic Effect of Oxytocin," on pages 225–232.

Podocyte-Specific Gene Mutations Are Coming of Age

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J Am Soc Nephrol 19: 190–191, 2008.

doi: 10.1681/ASN.2007121341

Major leaps have been made recently in the understanding of the cause of proteinuria and hence in the regulation of glomerular permeability in health. Progress has been fueled by the description of single-gene mutations, the majority of which affect genes expressed selectively in the podocyte, resulting in nephrotic syndrome in human and mouse.¹ This has placed the podocyte center stage as a key regulator of normal selective permeability to albumin in the glomerular capillary wall, although we should not forget that single-gene mutations affecting components of the glomerular basement membrane can also result in heavy proteinuria,² or that the third component of the glomerular capillary wall, the glomerular endothelial cell, can also play an important role in regulating glomerular permeability in health and disease.³

The first podocyte-specific gene identified by studying disease-associated mutations was *NPHS1*, encoding nephrin⁴; this was swiftly followed by identification of *NPHS2*, encoding podocin,⁵ also a novel protein important in the structure and function of

Published online ahead of print. Publication date available at www.jasn.org.

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glomeruli.⁶ Since the discovery of nephrin and podocin, several other disease-associated podocyte-specific gene defects have been reported, and, undoubtedly, there will be more to come.

Mutations in different podocyte genes or different mutations in the same gene result in varying phenotypes regarding severity and age of onset of proteinuria, and it is clear that there are likely to be other disease-modifying genes or environmental influences. Moreover, congenital forms of nephrotic syndrome are rare, and a question that intrigues nephrologists and basic scientists alike is whether the more common forms of sporadic, often later onset nephrotic syndrome could also be associated with mutations or polymorphisms in podocyte-specific genes, as predisposing factors or contributors to a complex etiology involving genetic–environmental interactions. If so, then study of these genes could be clinically useful in diagnosis and prognosis, especially concerning the likelihood of corticosteroid responsiveness and the issue of likely recurrence in renal transplants for patients who progress to end-stage renal failure.

The article in this issue of *JASN* by Hinkes *et al.*,⁷ the product of an impressive multinational collaboration, sheds light on these issues. The study amassed 430 patients with steroid-resistant nephrotic syndrome, the vast majority of whom were the only affected family member, although the series did include 23 families with more than one affected member. The patients were screened for mutations in *NPHS2* by direct sequencing of all eight exons of the gene. Eighty-two patients (19% of the total) had mutations in *NPHS2*. In the families with more than one affected member, the proportion with *NPHS2* mutations rose to 39%. In patients with two *NPHS2* mutations, the authors report that approximately 40% had one truncating (frameshift or nonsense) mutation and an additional 30% had homozygous *R1308Q* mutations (the “founder” *NPHS2* mutation identified by Boute *et al.*⁵). These two groups of individuals nearly all developed nephrotic syndrome at an early age (<6 yr, with a mean age of onset <2 yr). The remaining 30% of patients with other mutations or variants in *NPHS2* had later onset disease without any further specific link between any given genotype and age of onset (although the numbers of patients with each genotype were small). Mutation type did not affect rate of deterioration, time from onset to ESRD being the same in all groups.

Although this represents real progress, even within the groups with early presentation there was still a wide range of age of onset. Also, >80% of the collection with steroid-responsive nephrotic syndrome did not have any abnormality of *NPHS2*, so their proteinuria remains unexplained; clearly there is more work to be done.

The power of large multinational studies such as this one will be essential if analyses of genotype–phenotype relationships in nephrotic syndrome are to yield informative conclusions. Ideally, genetic analysis should be more widely available as a diagnostic and prognostic aid in patients presenting with nephrotic syndrome; however, at present, clinicians will need further guidance from geneticists about the interpretation of genotype–phenotype relationships. Hinkes *et al.* are to be congratulated for leading the way.

DISCLOSURES

None.

REFERENCES

1. Tryggvason K, Patrakka J, Wartiovaara J: Hereditary proteinuria syndromes and mechanisms of proteinuria. *N Engl J Med* 354: 1387–1401, 2006
2. Zenker M, Aigner T, Wendler O, Tralau T, Müntefering H, Fenski R, Pitz S, Schumacher V, Royer-Pokora B, Wühl E, Cochat P, Bouvier R, Kraus C, Mark K, Madlon H, Dötsch J, Rascher W, Maruniak-Chudek I, Lennert T, Neumann LM, Reis A: Human laminin beta2 deficiency causes congenital nephrosis with mesangial sclerosis and distinct eye abnormalities. *Hum Mol Genet* 13: 2625–2632, 2004
3. Ballermann BJ: Contribution of the endothelium to the glomerular permselectivity barrier in health and disease. *Nephron Physiol* 106: 19–25, 2007
4. Kestila M, Lenkkeri U, Mannikko M, Lamerdin J, McCready P, Putaala H, Ruotsalainen V, Morita T, Nissinen M, Herva R, Kashtan CE, Peltonen L, Holmberg C, Olsen A, Tryggvason K: Positionally cloned gene for a novel glomerular protein—nephrin—is mutated in congenital nephrotic syndrome. *Mol Cell* 4: 575–582, 1998
5. Boute N, Gribouval O, Roselli S, Benessy F, Lee H, Fuchshuber A, Dahan K, Gubler MC, Niaudet P, Antignac C: *NPHS2*, encoding the glomerular protein podocin, is mutated in autosomal recessive steroid-resistant nephrotic syndrome. *Nat Genet* 24: 349–354, 2000
6. Huber TB, Schermer B, Benzing T: Podocin organizes ion channel-lipid supercomplexes: Implications for mechanosensation at the slit diaphragm. *Nephron Exp Nephrol* 106: e27–e31, 2007
7. Hinkes B, Vlangos C, Heeringa S, Mucha B, Gbadegesin R, Liu J, Hasselbacher K, Ozaltin F, Hildebrandt F, members of the APN Study Group: Specific podocin mutations correlate with age of onset in steroid-resistant nephrotic syndrome. *J Am Soc Nephrol* 19:365–371, 2008

See related article, “Specific Podocin Mutations Correlate with Age of Onset in Steroid-Resistant Nephrotic Syndrome,” on pages 365–371.

The Disadvantage of Being Fat

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J Am Soc Nephrol 19: 191–193, 2008.
doi: 10.1681/ASN.2007121337

Given the epidemic of obesity in the United States, it is not surprising that an increasing fraction of patients who are considered for and receiving kidney transplants are also overweight. Friedman *et al.*¹ found a 41.9% decrease in the fraction

Published online ahead of print. Publication date available at www.jasn.org.

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