TRANSPLANTATION

A simple test for PVN

A simple and noninvasive urine test can be used to diagnose BK polyomavirus nephropathy (PVN), a serious infectious complication seen mainly in renal allograft recipients, say researchers in the US.

As no specific therapies to treat PVN are currently available, patients' outcomes depend largely on the stage of disease at the time of diagnosis, and early and accurate detection is, therefore, very important. "Current clinical assays for monitoring signs of BK polyomavirus replication in the urine and plasma are not specific for intrarenal disease and show high interlaboratory variation," explains lead investigator Volker Nitsch. "Even renal biopsies—the gold standard for PVN diagnosis—can give false negative results in some cases."

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Previously, the researchers had found that existing tools for diagnosing PVN from urine samples (for example, quantification of decoy cell shedding by cytology, measurement of viral loads by polymerase chain reaction, and negative-staining electron microscopy) were equally sensitive. They noticed, however, unusual

three-dimensional cast-like polyomavirus aggregates in some urine samples analyzed by negative-staining electron microscopy. These aggregates—which they named 'Haufen' after the German word for 'cluster' or 'stack'—appeared only in the urine of patients with biopsy-confirmed PVN.

In the current study, Singh and colleagues analyzed 194 urine samples from 139 control patients without evidence of PVN and 143 samples from 21 patients with biopsy-confirmed PVN. They used conventional cytology to detect decoy cells in urine, quantitative polymerase chain reaction to assess BK viral loads in plasma and urine, and negative-staining electron microscopy to identify Haufen in urine. The researchers found Haufen in urine samples from all 21 patients with PVN at various stages of disease, but not in any urine samples from control patients. By contrast, they noted high levels of viremia in 8% of control patients and substantial viruria in 41% of controls. Detection of Haufen in urine correlated strongly with biopsy-confirmed PVN (concordance rate 99%). The qualitative detection of Haufen was 100% sensitive and 99% specific for the presence of biopsy-confirmed PVN; the positive predictive value was 97% and the negative predictive value was 100%. In addition, the researchers found that Haufen did not lose their characteristic ultrastructural

features when fixed and stored at 4 °C for 3–15 months; thus, fixed urine samples could be sent to outside laboratories for testing.

According to the researchers, the new and most promising aspect of the findings is that as Haufen seem to originate in virally injured renal tubules, their presence in voided urine samples can serve as a direct marker of intrarenal disease (that is, PVN). "This concept is novel and differs sharply from [those of] existing screening assays that are based on detection and quantitation of polyomavirus replication, which is not necessarily diagnostic for renal disease," states Nitsch. At present, the researchers are performing further prospective studies to validate their retrospective observations. They hope that Haufen, as noninvasive markers of PVN, will aid the evaluation of new antiviral drugs and assist the accurate diagnosis of disease and/or complications in patients receiving immunosuppressive drugs.

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Original article Singh, H. K. *et al.* Presence of urinary Haufen accurately predicts polyomavirus nephropathy. *J. Am. Soc. Nephrol.* 20, 404–415 (2009).