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GLOMERULAR DISEASE

Bovine serum albumin: involved in childhood membranous nephropathy?

Bovine serum albumin (BSA) derived from cow's milk may be involved in the pathogenesis of membranous nephropathy in some children, according to a study recently published in the *New England Journal of Medicine*.

"For the past 10 years, we have been interested in identifying target antigens involved in membranous nephropathy," notes corresponding author, Hanna Debiec of Tenon Hospital, Paris, France. "Our aim was to find new pathophysiological bases for innovative treatments. Following the identification by our group of neutral endopeptidase as the target antigen in allo-immune neonatal membranous nephropathy, and the findings by Beck and colleagues showing that the M-type phospholipase A_2 receptor (PLA_2R) is the target antigen in about two-thirds of cases of adult idiopathic membranous nephropathy, we decided to search for additional antigens in other patient groups. In the wake of studies devoted to childhood membranous nephropathy, we tested whether sera in such patients contained antibodies directed to additional antigen specificities. We became interested in BSA because of the possible implication of anti-BSA antibodies in other autoimmune diseases and in an experimental model of membranous nephropathy in the rabbit some 30 years ago."

Debiec *et al.* used enzyme-linked immunosorbent assay (ELISA) and Western blotting to search for antibodies against BSA and circulating BSA in serum specimens from 50 patients with membranous nephropathy (nine of whom were children) and 172 controls (63 age-matched patients with other glomerular diseases and 109 controls without proteinuria). They found high levels of circulating anti-BSA antibodies in seven adults and four children. Two controls also had high levels of anti-BSA antibodies.

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Using two-dimensional sodium dodecyl sulfate–polyacrylamide gel electrophoresis, the researchers investigated the properties of immunopurified circulating BSA obtained from serum samples. They found that the four children who had membranous nephropathy and high levels of anti-BSA antibodies also had high levels of cationic circulating BSA. Four of the seven adults with membranous nephropathy and high levels of anti-BSA antibodies also had increased levels of circulating BSA (although lower levels than those in the four children). By contrast, levels of circulating BSA were very low in the two controls with high levels of anti-BSA antibodies.

Debiec *et al.* also analyzed cryosections or paraffin-embedded sections of normal human kidney and biopsy specimens obtained from patients with membranous nephropathy and patients with other glomerular diseases. Subepithelial granular deposits of BSA were present only in children with high levels of circulating cationic BSA and anti-BSA antibodies. Kidney biopsy specimens from normal kidneys and kidneys from patients with other glomerular diseases were negative for BSA, and no staining was seen in biopsy specimens from patients with idiopathic membranous nephropathy but without circulating cationic BSA, regardless of the presence or absence of anti-BSA antibodies. M-type PLA_2R was absent in glomerular immune deposits in biopsy specimens from patients with positive staining for BSA, but present in 14 of 20 specimens from patients without BSA deposits. The authors state that these results indicate that four of the children had membranous nephropathy caused by circulating cationic BSA. "The BSA was cationic only in children with high levels of BSA, whereas BSA in adults who had circulating BSA had a normal charge close to neutrality," notes Pierre Ronco, another researcher on the study. "Because the BSA was cationic in children, it could become trapped or implanted in the glomerular capillary wall that carries opposite (anionic) charges."

"In the future, we want to understand why an undigested form of cationic BSA circulates in some young children and to identify the source of the antigen, which may be some cow-milk-derived formulas or the transformation of BSA by the microbiotic intestinal flora, or both," states Debiec. "We also want to identify other food and environmental antigens that might be involved in immunologically mediated nephropathies."

Rebecca Ireland

Original article Debiec, H. *et al.* Early-childhood membranous nephropathy due to cationic bovine serum albumin. *N. Engl. J. Med.* **364**, 2101–2110 (2011)

Further reading Beck, L. H. Jr *et al.* M-type phospholipase A_2 receptor as target antigen in idiopathic membranous nephropathy. *N. Engl. J. Med.* **361**, 11–21 (2009)