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Association of humoral immunodeficiency, cleidocranial dysplasia, and von Willebrand's disease in a family cluster

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To the Editor:

We present a cluster of 3 family members with primary immunodeficiency associated with cleidocranial dysplasia (CCD) and von Willebrand's disease (VWD). We evaluated a 16-year-old female patient with a medical history significant for *Pneumocystis carinii* pneumonia and cytomegalovirus hepatitis at 4 months of age, recurrent pneumonia episodes complicated with empyema and *Streptococcus pneumoniae* sepsis, otitis media, sinusitis, periorbital cellulitis, recurrent upper respiratory tract infections, VWD, CCD, and patent ductus arteriosus. Her immunologic evaluation revealed normal serum Ig levels, IgG subclasses, neutrophil chemoluminescence and chemotaxis, complement activity, and in vitro IL-2 production, and negative HIV serology. Lymphocyte blastogenesis to mitogens and antigens was slightly diminished compared with that of a normal control subject. Humoral studies showed normal antibody response to protein antigens but absent response to polysaccharide antigens. These findings were consistent with specific antipolysaccharide antibody deficiency. The patient's sister had a history of recurrent pneumonia, otitis media, tonsillitis, VWD, and CCD. Findings of her immunologic evaluation including serum Ig levels, IgG subclasses, and lymphocyte surface markers were normal. The functional humoral studies were not done because she died at 18 years of age of pneumococcal pneumonia

and sepsis. Her mother also had VWD and CCD and showed a very poor humoral response to Pneumovax but did not have a significant history of infections.

Ritscher-Schinzel syndrome shares some craniofacial features with CCD and is associated with congenital heart defects and hypogammaglobulinemia, but it is distinguished by other malformations including Dandy-Walker malformation, which was absent in our patient.¹

One patient with Baller-Gerold syndrome has been reported as having craniosynostosis and immunodeficiency consisting of profound hypogammaglobulinemia with significant reduction of circulating B cells and strikingly diminished levels of all serum Ig isotypes. Results of the chromosomal analysis were normal.²

Impaired antibody responses to polysaccharide antigens occur in patients with primary immune deficiencies such as ataxia-telangiectasia syndrome, Wiskott-Aldrich syndrome, and common variable immunodeficiency. Except for IgG2 deficiency, these primary immune deficiencies also have impaired responses to protein antigens. Ambrosino et al^{3,4} described patients who had abnormal responses to immunization with polysaccharides such as *Haemophilus influenzae* type b capsular antigen or to the pneumococcal polysaccharide antigens but who had normal serum Ig and IgG subclass concentrations.

This is the first report of a primary immunodeficiency associated with CCD and VWD in a family cluster. CCD is clearly segregating as an autosomal dominant condition in this family and affected the patient, her sister, her mother, and probably 2 maternal uncles and a maternal grandfather (Fig 1). VWD appears to be segregating independently from the CCD, and the patient's sister and mother are affected, but other family members are not. There was nothing in this patient's history to explain her apparently high number of infections. The chromosomal location of CCD is unknown. Patients with these conditions are at risk for passing both traits on to their children. Because of the dominant nature of these conditions, with each pregnancy patients face a 25% risk for passing on both traits, a 50% risk for passing on only 1 of the traits, and a 25% risk of passing on neither trait.

In addition to the above genetic diseases, the 3 patients presented here had an immune deficiency consisting of defective functional antibody response selective to polysaccharide antigens. This was a T-cell-independent humoral response and was associated with normal serum Ig levels and a normal humoral response to protein antigens (T cell dependent). The genetic defect responsible for antipolysaccharide antibody deficiency is not known. In most cases, this particular disorder occurs sporadically at a variable age of onset. However, in this report, the presence of this immunodeficiency in 3 family members since early childhood strongly suggests a primary common genetic defect. In addition, the association of immunodeficiency with 2 other congenital disorders may give some insight into future studies for the localization of the specific gene involved in T-cell-independent humoral responses.

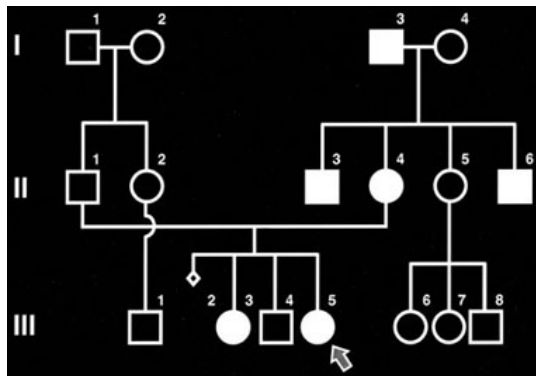
In conclusion, this is the first report of a primary immunodeficiency associated with CCD and

VWD in a family cluster. This may well be the first report of a new syndrome.

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Fig. 1. Pedigree of the patient. *Solid squares and circles indicate family members with CCD, VWF, and infection. Arrow indicates the patient.*



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