Is microalbuminuria progressive?

We read with interest the article by Shields et al on the question whether microalbuminuria is progressive or not.1 Our data, presented at the 21th Annual Meeting of the ISPAD in Linköping,2 are fully in line with the conclusions of this work. In 1984 we identified 14 children and adolescents as having persistent microalbuminuria (urinary albumin excretion (UAE) 30–300 μg/day) with insulin dependent diabetes mellitus (median age = 15.2 years; median duration of diabetes = 5.7 years). Eight cases showed HLA DR3-DRA4. A regular follow up for six years of these microalbuminuric patients allowed us to follow their progression: two developed macroalbuminuria, five remained microalbuminuric without presenting a significant increase in UAE, and seven remained stably normal, after a period of microalbuminuria of between 1 and 5.5 years. These latter patients did not differ from those remaining microalbuminuric either as regards degree of metabolic control or UAE levels during follow up, whereas they did differ as regards a higher prevalence (6/7) of cases with onset of diabetes in peripubertal age. Shield et al did not report data regarding age or pubertal stage of the single microalbuminuric patients; we feel this finding could be important in that it could be the pubertal factor which differentiates the natural history for microalbuminuria in childhood from that of adulthood. Puberty, with its important hormonal changes, could in fact act as ‘exercise test’ for the kidney of predisposed subjects; this would lead to a deterioration which, limited to the pubertal period, would be temporary. Supporting this hypothesis is the fact that six of our 10 patients (all females) with intermittent microalbuminuria, occurring at the beginning of puberty, reverted to normal at the end of puberty itself, that is after menarche.

The predictive value for later overt nephropathy, microalbuminuria is therefore poor among children and young adults and this possible spontaneous normalisation of microalbuminuria should be taken into ac-
count when evaluating the effects of interventional drug treatment in patients of this age.

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Dr Shield comments:

This report is now the third to challenge the predictive value of microalbuminuria defined as 20–200 μg/min (30–300 mg/day) in childhood and adolescence as a recent article from Rudberg and Dahlquist reached similar conclusions.3 The implications of microalbuminuria in this age group need to be addressed prospectively in a large cohort of patients before embarking on either routine clinical screening or interventional trials. A study (microalbuminuria in diabetic adolescents and children, MIDAC), currently in the pilot stage, will address the prevalence and progression of abnormal albumin excretion in approximately 2000 children with diabetes with glycaemic control, blood pressure, and pubertal status which we agree may be of importance in defining the longer term significance of microalbuminuria.


Mycoplasma infection and Kawasaki disease

We report for the first time a case of mycoplasma infection complicated by Kawasaki disease, and discuss possible mechanisms.

A 6 year old boy presented with two days of sore throat, fever, vomiting, and abdominal pain. Examination revealed pharyngitis and cervical lymphadenopathy. Jaundice and tender hepatomegaly developed the next day. Investigations revealed a leucocytosis (white cell count 18.7 × 10⁹/l), deranged liver function (bilirubin concentration 73 μmol/l, alanine transaminase activity 316 units/l), and positive immunofluorescence for IgM to Mycoplasma pneumoniae, with a fourfold rise in antibody titre to greater than 256. Testing for other causes of hepatitis was negative. Mycoplasma hepatitis was diagnosed, and treatment with azithromycin started.

His fever persisted, and bilateral conjunctivitis, raised erythrocyte sedimentation rate (ESR) (maximum 125 mm/hour), thrombocytosis (maximum 846 × 10⁹/l) on day 9, dished gall bladder on ultrasound scan on day 11 and perianual desquamation developed on day 17. No cardiac ultrasound examination was normal.

Kawasaki disease was diagnosed, based on the persistent fever, pharyngitis, cervical lymphadenopathy, bilateral conjunctivitis, raised ESR, thrombocytosis, and eventual perianual desquamation. A distended gall bladder on ultrasound scan is found in 3% of patients with Kawasaki disease.1 Treatment with intravenous
immunoglobulin and oral aspirin was started, the patient recovered and was discharged on day 25. Follow up at one year is normal.

The aetiology of Kawasaki disease is unclear, but superantigens may play a part. By interacting directly with class two major histocompatibility complex molecules, superantigens can stimulate polyclonal T cell activation with subsequent massive cytokine release. Mycoplasma arthritidis has been shown to produce superantigens, and it is therefore possible that other mycoplasma organisms may do likewise. Superantigen is also produced by staphylococci, streptococci, and retroviruses, all of which have been associated with cases of Kawasaki disease. However, to our knowledge no reports of Kawasaki disease related to mycoplasma infection have been recognised.

We postulate that the development of Kawasaki disease after mycoplasma infection in this patient may have been due to the production of superantigen by the mycoplasma organism.

**BCG and prevention of tuberculous meningitis**

Thilothammal and colleagues' case-control study on the effectiveness of BCG vaccine in preventing tuberculous meningitis was well conducted and did discuss the possibility of biases, but left some points that deserve clarification and discussion, as they may affect the validity of the results.

Firstly, it is unclear whether the authors accounted for matching in their analysis, as they did not mention it. The appropriate multivariate analysis technique applicable to matched case-control studies is conditional logistic regression, and the use of unconditional logistic regression for matched data bias the odds ratio towards the null. In this study it would have therefore underestimated BCG effectiveness.

Secondly, children with febrile convulsions may not have been the best possible control group, as apparently the catchment areas were not the same for cases and controls (in the paper the authors argue that neighbourhood controls would have been best, but unfeasible as 'cases coming from different parts of the state was a limiting factor'). Selection bias may have occurred if the study bases (catchment areas) were different, and bias would have been towards over or under-estimation of BCG effectiveness depending whether the BCG coverage was respectively lower or higher in the catchment area of cases as compared to the catchment area of controls.

Finally, the provided explanations for the lack of effectiveness of BCG in preventing tuberculous meningitis in the 8–12 years age group are all plausible. Further exploration of this finding will be of considerable interest, especially if waning of immunity is the true reason, as this information can be useful when considerations about the need and the optimal timing for a second dose of BCG aiming at prevention of tuberculous and/or leprosy are made.

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Dr Thilothammal and coauthors comment:

Each case was not matched with controls as a set. But, block matching was done for the age, in order to have equal number of cases and controls in each age group. Matching was not taken into consideration in the logistic regression analysis.

Though the controls were selected from the hospital, the demographic parameters like type of house, maternal education, nutritional status, and crowding in the house were comparable between cases and controls indicating that both groups have probably arisen from similar population.

We agree with Dr Nishioka that further studies in children of an older age group will be both interesting and useful in guiding policies regarding BCG vaccination.


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