PostScript

LETTERS

Effects of probiotics on atopic dermatitis? Additional studies are still needed!

We read with interest the paper by Weston *et al* of a well designed and well carried out trial on the effects of probiotics in schoolchildren with atopic dermatitis.[1] We have two methodological questions related to the authors' conclusions.

First, in the discussion section the authors claim that this is the first study to show a benefit following administration of probiotics in children with moderate to severe atopic dermatitis. In our opinion this conclusion is not supported by the data generated by this study. Our main reason is that most changes in outcome found refer to changes *within* treatment groups and not differences *between* treatment groups. In a placebo controlled trial, changes *within* the intervention (probiotic) group may indicate a beneficial effect, but could also be due to a beneficial change in the course of the disease over time, regardless of the intervention. Therefore, a placebo group is included to control for the natural course of the disease (in this case atopic dermatitis). Hence, proof of a beneficial effect of the treatment can only be given when a difference *between* groups is found. In the Weston *et al* study, most changes are found *within* the intervention group and not *between* the two treatment groups; therefore we think that their findings merely suggest, but do not prove, that probiotics have a beneficial effect in schoolchildren with moderate eczema.

Second, in the same section, it is stated that this is the first study to show persisting benefits two months after supplementation ceased. This study consisted of a treatment period of eight weeks with a follow up period of eight weeks after the treatment was stopped. A prerequisite to make the above mentioned statement at the 16 weeks' time point, is that blinding for the assessing physician (in the case of objective outcome criteria) and for the participants and their parents (in the case of subjective outcome criteria) is maintained. Since the randomisation code is usually broken at the end of the treatment phase and as this is not mentioned in the text, we wonder if this specific prerequisite was fulfilled. If this is not the case, in our opinion this conclusion must be toned down.

M O Hoekstra, L E M Niers
Paediatric Allergology Clinic, Wilhelmina Children's Hospital, University Medical Centre Utrecht, PO Box 85090, 3508 AB Utrecht, Netherlands; mohoekstra@hetnet.nl

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Reference

1 **Weston S**, Halbert AR, Richmond P, *et al*. Effects of probiotics on atopic dermatitis: a randomised controlled trial. *Arch Dis Child* 2005;**90**:892–7.

Authors' reply

Hoekstra *et al* have raised questions regarding the conclusion from our recent randomised control trial of the effects of probiotics on the severity of atopic dermatitis in young children. Our findings suggested a clinical benefit albeit a modest one. This conclusion was based on both "between group" differences at the end of the study as well as "within group" changes over the course of the study. We agree with the importance of examining the differences between groups at the end of treatment and the end of the follow up. These analyses were performed and included in the initial submission of our manuscript. We noted that total SCORAD was significantly lower in the probiotic group (median 24.4) compared with the placebo group (36.3) at week 16 ($p = 0.019$ determined by Mann-Whitney test). A similar but non-significant difference was seen at 8 weeks ($p = 0.119$). While these analyses were included in the initial draft, one of the reviewers reasonably suggested that the data were presented in terms of the "changes from baseline", and we revised the manuscript accordingly. We also received independent statistical advice to that effect. As there are arguments to examine the data in both ways, we have elected to show the raw data for the group comparison here in fig 1. These differences are consistent with the within group differences seen between probiotic and control groups reported in the paper. Using a logistic regression model, children in the probiotic group were seven times more likely to show improvement of symptoms following probiotic supplementation than those on placebo (odds ratio = 7.06; 95% CI 1.37 to 36.4; $p = 0.02$).

Contrary to the suggestions of Hoekstra *et al*, both the subjects and investigators remained "blind" to the intervention until all the data collection was completed for all visits (including the 16 week follow up visit).

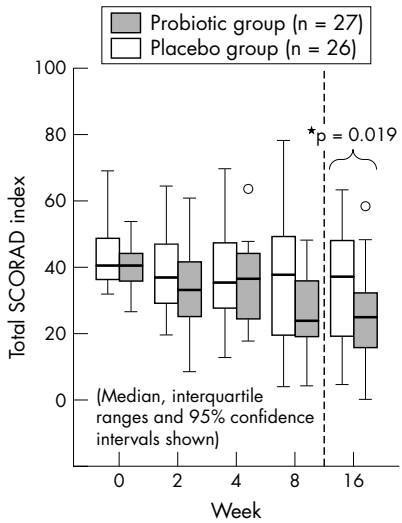

Figure 1 SCORAD Index over the study period: including baseline (week 0), the supplementation period (weeks 2–8), and 8 weeks after ceasing supplementation (week 16).

We agree that additional studies are needed to confirm these findings in a larger population as well as having a longer follow up to ensure that the beneficial effects seen up to 4 months persist in the long term. We are also interested in the immunological effects, and whether the benefits seen may also translate into a reduced risk of subsequent aeroallergen sensitisation and development of allergic rhinitis and asthma that become frequent problems in children with moderate to severe AD.

S Prescott, P Richmond, S Weston, A Halbert
Princess Margaret Hospital, PO Box D184, Perth 6008, Australia; susanp@ichr.uwa.edu.au

Incomplete Kawasaki disease: not to be forgotten

Drs Sinha and Balakumar have provided a reminder of BCG scar reactivation as a diagnostic marker of Kawasaki disease (KD).[1] This potentially serious disease has no definitive diagnostic test and it is not unusual for the diagnosis to be delayed. The authors also alluded to incomplete KD, of which there is increasing recognition and which may be associated with a higher chance of cardiac complications.[2]

We recently reviewed the cases of KD presenting in South Wales and found an alarming increase in the number of patients developing coronary artery aneurysms in comparison to a similar review done in 2001. In 2001 the Paediatric Cardiac Unit at the University Hospital of Wales presented a 10 year audit of KD. We reported 57 cases in 10 years and only three patients had coronary artery aneurysms. Since that audit was undertaken we are aware of 27 more cases of KD in the last four years. The incidence of the disease therefore does not appear to have changed, however we are now seeing a higher incidence of coronary artery abnormalities (observed in 10 of the 27 cases). This includes both medium sized and giant coronary artery aneurysms. Remarkably, in one infant the diagnosis of KD was made retrospectively when an echocardiogram for an unrelated reason showed giant coronary artery aneurysms.

Although the reason for this apparent increase in the incidence of coronary artery abnormalities remains unclear, it highlights the importance of considering the diagnosis of KD in any infant or child with high grade fever for five or more days. This is especially true in younger infants who are at a higher risk of developing coronary artery aneurysms and who may present with fever and few if any of the cardinal clinical features of KD. In fact the latest guidelines by the American Heart Association recommend that echocardiography should be considered in any infant aged less than 6 months with fever of seven days or more in duration and laboratory evidence of systemic inflammation.[3]

A variety of helpful diagnostic clues have been recognised over the last few years. Notable is the presence of hydrops of gall

bladder in 15% of the cases which can be picked up easily on an abdominal ultrasound.[4] Arthritis and arthralgia generally involving multiple small joints in the first week and large weight bearing joints later can occur. Up to a third of these patients have gastrointestinal symptoms such as diarrhoea, vomiting, and abdominal pain and rarely KD may present as acute surgical abdomen.[5] Transient unilateral facial nerve palsy and high frequency sensori-neural hearing loss may also occur.[6]

The report by Drs Sinha and Balakumar is a timely reminder to be vigilant for this potentially dangerous disease with protean manifestations.

A Gandhi, D G Wilson
Children's Heart Unit for Wales, University Hospital of Wales, Heath Park, Cardiff CF14 4XR, UK; anjumgandhi@aol.com

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Re: The implications of the David Glass case for future clinical practice in the UK

Hindsight is both a wonderful and a dreadful thing. Although outside the scope of Elias-Jones and Samanta's article,[1] was David's tonsillectomy necessary in the first place [for ''noisy and laboured breathing'']? Have those who made the referral and who agreed to carry out the operation reviewed whether it was the right thing to do? Were the referral and operation done because of pressure from, for example, professionals involved with the child yet who in no way carried any consequences for subsequent events?

We always need to remember the Ulysses syndrome—patients who are caught in a web of investigations, referrals, and treatment which may not have been necessary in the first place.[2]

C Essex
Child Development Unit, Gulson Hospital, Coventry Primary Care NHS Trust, Coventry CV1 2HR, UK; room101@ntlworld.com

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Risk of hypertension in children with multicystic dysplastic kidney

The power of a systematic review is only as good as the question being posed. In his review of the risk of hypertension in children with multicystic kidney disease (MCKD), Narchi misses the wider context.[1] There may be more than one relationship between the diagnosis of MCKD and blood pressure (BP). Perhaps the component in the mind of the author is that a multicystic dysplastic kidney might in itself be a cause of hypertension. This seems unlikely if the affected kidney is non-functioning and contains no renal elements. His review supports this presumption, although exceptions are clearly reported.[2] The majority of non-functioning multicystic dysplastic kidneys involute, so that a proportion of individuals who had MCKD originally are diagnosed later as having unilateral renal agenesis (RA), technically a misnomer in this case. It would make more sense to widen the enquiry to include this category.

An important consideration is the role of the *contralateral* kidney in the regulation of BP in these patients. Firstly, the contralateral kidney will prove to be radiologically abnormal in about a quarter of cases of MCKD or RA. Coarse focal scarring, hydronephrosis, or hypoplasia would be expected to have an impact on BP depending on the nature of the abnormality.

Radiologically normal solitary kidneys can also predispose to hypertension. Although they are significantly larger than normal paired kidneys and their complement of nephrons is unknown, there are good reasons to consider that patients with MCKD or RA embark on life with a reduced number of nephrons. There are data to indicate that a modest reduction in the number of nephrons, even in people with two kidneys, is a risk factor for the development of hypertension.[3 4] This is supported by studies in other species, and in a variety of models.[5–7] For example uni-nephrectomy in rat pups and in the ovine fetus induces salt sensitive hypertension that takes time to evolve.

Blood pressure is a continuous variable in the population, and correlations between BP and cardiovascular disease extend well into the normal range.[8] Therefore the separation of hypertension from normotension is somewhat arbitrary, and the qualitative end point does not serve the analysis very well, particularly in young subjects who have yet to disclose overt hypertension however defined. A correlation with the quantitative variable of blood pressure is more relevant. Omitted from the review is the observation that a subtle but significant increase in BP can be found in children with a solitary kidney using 24 hour ambulatory BP recording.[11] Moreover, there are enough follow up studies of adults with either unilateral RA or surgical loss of one kidney in childhood to suggest an increase risk of hypertension even when the remaining kidney is thought to be ''normal''.[9 10] It clearly takes time, certainly more than 20 years, for this end point to be reached.

Narchi's plea for long term follow up is a sound one but should not be based on the premise that there is no information on outcome. On the contrary, there is enough positive information to indicate that individuals with MCKD, RA, or renal loss for other reasons early in life deserve BP monitoring in adulthood, especially if there are additional risk factors such as obesity.[12]

C M Taylor
Correspondence to: Department of Nephrology, Birmingham Children's Hospital, Birmingham B4 6NH, UK; cm.taylor@bch.nhs.uk

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Author's reply

We can reassure Taylor that the wider context of hypertension associated with multicystic dysplastic kidney (MCDK) was not missed in this review, for the following reasons:

(1) The purpose of the review was to quantify the risk of hypertension associated with a unilateral MCDK based on longitudinal cohort studies, irrespective of the mechanism(s) for that hypertension, and which single case reports definitely cannot answer. We are therefore confident that all cases, regardless of their theoretical pathophysiology for hypertension, have been included. Interestingly, the case reports cited by Taylor seem to invalidate his statement that the absence of renal elements in the non-functioning MCDK makes it unlikely to be the cause of hypertension, as most showed that nephrectomy of the dysplastic kidney led to normalisation of the blood pressure. These simple clinical observations highlight how much we do not know despite the numerous theories and animal experiments extensively referenced by Taylor.

(2) Taylor correctly reminds us that abnormalities in the contralateral kidney probably increase the risk of hypertension. This is exactly why, in an attempt to quantify the risk of a single affected kidney, only unilateral MCDK with a radiologically normal contralateral