Effect of Pentavac and measles-mumps-rubella (MMR) vaccination on the intestine

B Thjodleifsson, K Davídsdóttir, U Agnarsson, G Sigthórsson, M Kjeld and I Bjarnason

Gut 2002;51;816-817
doi:10.1136/gut.51.6.816

INFLAMMATION AND INFLAMMATORY BOWEL DISEASE

Effect of Pentavac and measles-mumps-rubella (MMR) vaccination on the intestine

B Thjodleifsson, K Davídsdóttir, U Agnarsson, G Sigthórsson, M Kjeld, I Bjarnason

Gut 2002;**51**:816–817

See end of article for authors' affiliations

Correspondence to: Professor I Bjarnason, Department of Medicine, Guy's, King's, St Thomas' Medical School, Denmark Hill Campus, Bessemer Road, London SE5 9PJ, UK; ingvar.bjarnason@kcl.ac.uk

Accepted for publication 15 May 2002

Background: The safety of infant vaccination has been questioned in recent years. In particular it has been suggested that the measles, mumps, and rubella (MMR) vaccination leads to brain damage manifesting as autism consequent to the development of an "enterocolitis" in the immediate post-vaccination period.
Aim: To assess if MMR vaccination is associated with subclinical intestinal inflammation, which is central to the autistic "enterocolitis" theory.
Methods: We studied 109/58 infants, before and two and four weeks after immunisation with Pentavac and MMR vaccines, for the presence of intestinal inflammation (faecal calprotectin).
Results: Neither vaccination was associated with any significant increase in faecal calprotectin concentrations.
Conclusions: The failure of the MMR vaccination to cause an intestinal inflammatory response provides evidence against the proposed gut-brain interaction that is central to the autistic "enterocolitis" hypothesis.

The presence of lymphoid nodular hyperplasia and colitis in autistic children, termed autistic "enterocolitis", with various gastrointestinal symptoms investigated a number of years after immunisation is not in doubt.[1 2] However, the aetiology and pathogenesis of the intestinal inflammation is controversial[3] as is the possible role of the intestine in the development of the central nervous system dysfunction that may manifest in mental health disorders.[4 5]

One hypothesis of the pathophysiology of autistic "enterocolitis" postulates that the measles vaccination virus of the measles, mumps, and rubella (MMR) vaccine escapes initial detection by the immune system[3] and disseminates to the intestinal lymphoid tissue. Here, it is suggested, it leads to an "enterocolitis" with increased permeation of neurotoxic luminal substances during a vulnerable part of brain development, leading to regressive autism.[3 6] Central to this hypothesis is the development of intestinal inflammation in the immediate period following vaccination.

We tested this hypothesis by assessing intestinal inflammation (faecal calprotectin) before and after Pentavac and MMR vaccination in a group of infants.

SUBJECTS AND METHODS

Iceland has a developed health service with a centralised vaccination programme that results in infant vaccination rates approaching 100%. Pentavac (Pasteur Mérieux, France) vaccination (against diphtheria, tetanus, pertussis, polio, *Haemophilus influenza* type b) is performed at three, five, and 12 months of age and MMR (Priorix; SmithKline Beecham) vaccination at 18 months. One hundred and nine infants attending two of the vaccination centres of Southwest Iceland participated. These were consecutive infants where the parents had been sent a pre-attendance information leaflet explaining the nature and aims of the research. All of those approached participated. No infant met the predetermined specific exclusion criteria to this study which included those specified by the makers of the vaccines, the presence of intestinal diseases, or ingestion of medications that are associated with intestinal permeability-inflammation.[7]

The infants were studied by measuring faecal calprotectin (Calprest, Calprotech Ltd, London, UK) one week before Pentavac (at 12 months of age) and MMR (at 18 months) vaccination, and two and four weeks later, respectively. Pentavac does not contain mercury, which has been proposed to predispose to the toxicity of MMR.[8] The pre-Pentavac measurement served as the normal reference range. The faecal calprotectin

Abbreviations: MMR, measles-mumps-rubella.

Table 1 Faecal calprotectin concentrations (mg/l) before and after Pentavac and measles-mumps-rubella (MMR) vaccination

	Pentavac			MMR		
	Pre	Post		Pre	Post	
	0 week	2 weeks	4 weeks	0 week	2 weeks	4 weeks
n	109	101	89	81	63	58
Median	39	40	37	36	38	46
Range	3–218	1–295	1–273	1–292	3–207	5–299

There were no significant differences between calprotectin levels at the different time points and sequential studies showed no significant changes following vaccination.

assay differs somewhat from many of the published ones,[9–12] mainly in the extraction procedure and amount of stool required for assay (200 mg rather than 5 g). The Calprest method gives calprotectin values that are approximately five times higher than the older method,[13] with improved sensitivity[14] for the detection of intestinal inflammation in adults.

All parents provided written informed consent and the studies were approved by the National University Hospital Ethics Committee.

RESULTS

Table 1 shows the median (range) values for faecal calprotectin concentrations in infants. There were no statistically significant differences in faecal calprotectin concentrations at any time points ($p>0.25$) (Friedman's two way analyses of variance) or when assessed in subjects studied before and after Pentavac ($p>0.2$) or MMR ($p>0.3$) vaccination (paired Student's *t* test on logarithmically transformed data which were normally distributed).

DISCUSSION

Naturally occurring measles viral infection has a predilection for the intestinal lymphoid tissue and may cause intestinal inflammation, which on occasions may resemble Crohn's disease.[15 16] The measles virus has controversially[17] been implicated in the pathogenesis of Crohn's disease[18–20] and other diseases, including multiple sclerosis.[21] The suggestion that the live attenuated measles vaccine might lead to ileocolonic inflammation with autistic features[1 2] has caused equal interest. This hypothesis was formulated in an attempt to explain the high prevalence of "enterocolitis" in autistic children with gastrointestinal symptoms.[1 6] Consequent to the measles vaccine virus induced ileocolonic inflammation, it is suggested, there is increased intestinal permeation of a variety of intestinally derived neuroactive peptides that interfere with brain development.[6 22–24] In support of this hypothesis are reports of intestinal pathology[1 2] and abnormal intestinal function in children with autism[25–27] when examined a number of years after the vaccination. These data are not particularly controversial but rather highlight the possible role and effect of the measles vaccination virus in the development of this inflammation in the immediate post-vaccination period and the postulated consequential effect on brain function.

In this study we specifically assessed the possibility that MMR vaccination leads to subclinical intestinal inflammation in infants undergoing immunisation. The upper limit of faecal concentrations of calprotectin (110 mg/l; 95% confidence limits (2 SD) calculated from logarithmically transformed mean data) before vaccinations at 12 and 18 months of age are comparable with published data in normal infants of the same age[28–30] and are twice as high as those reported in healthy adults. Pathological intestinal inflammation is easily differentiated from normal as faecal calprotectin values are usually well in excess of 1000 mg/l[28 29] under these circumstances.

There was no evidence that either Pentavac or MMR vaccination provoked subclinical intestinal inflammation in any of our apparently healthy children during the four week post-vaccination period. This lack of a detectable intestinal inflammatory response suggests that the measles vaccine virus itself is not enterotoxic in healthy infants which argues against the MMR induced autistic "enterocolitis" theory. This does not however rule out the possibility that vaccination might have an adverse effect on susceptible infants that are perhaps immune compromised or with an immunological makeup that predisposes them to autoimmune disease.[31]

ACKNOWLEDGEMENT

The study was supported by the Science Fund of the University Hospital Hringbraut Reykjavik and by Wyeth Lederle

Authors' affiliations

B Thjodleifsson, M Kjeld, Department of Medicine, University Hospital, Hringbraut, Reykjavík, Iceland
K Davídsdóttir, Center for Children Health Services, Reykjavík, Iceland
U Agnarsson, Center for Children Health Services, Reykjavík, and Sudurnes Health Institute, Keflavik, Iceland
G Sigthórsson, I Bjarnason, Department of Medicine, GKT Medical School, London, UK

REFERENCES

1 **Wakefield AJ**, Murch SH, Anthony A, *et al*. Ileal-lymphoid-nodular hyperplacia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998;**351**:637–41.
2 **Wakefield AJ**, Anthony A, Murch SH, *et al*. Enterocolitis in children with developmental disorders. *Am J Gastroenterol* 2000;**95**:2285–95.
3 **Halsey NA**, Hyman SL. Measles-mumps-rubella vaccine and autistic spectrum disorder: report from the new challenges in childhood immunizations conference convened in Oak Brook, Illinois, June 12–13, 2000. *Pediatrics* 2001;**107**:E84.
4 **Dohan FC**. Coeliac disease and schizophrenia. *Lancet* 1970;**i**:897–8.
5 **Wood NC**, Hamilton I, Axon ATR, *et al*. Abnormal intestinal permeability. An aetiological factor in chronic psychiatric disorders? *Br J Psychiatr* 1987;**150**:853–6.
6 **Wakefield AJ**, Puleston JM, Montgomery SM, *et al*. The concept of entero-colonic encephalopathy, autism and opioid receptor ligands. *Aliment Pharmacol Ther* 2002;**16**:663–74.
7 **Bjarnason I**, Macpherson AJM, Hollander D. Intestinal permeability: An overview. *Gastroenterology* 1995;**108**:1566–81.
8 **Ball LK**, Ball R, Douglas-Pratt R. An assessment of thimerosal use in childhood vaccines. *Pediatrics* 2001;**107**:1147–54.
9 **Tibble J**, Teahon K, Thjodleifsson B, *et al*. A simple method for assessing intestinal inflammation in Crohn's disease. *Gut* 2000;**47**:506–13.
10 **Tibble J**, Sigthorsson G, Fagerhol M, *et al*. Surrogate markers of intestinal inflammation are predictive for relapse in patients with inflammatory bowel disease. *Gastroenterology* 2000;**119**:15–22.
11 **Roseth AG**, Fagerhol MK, Aadland E, *et al*. Assessment of the neutrophil dominating calprotectin in feces. A methodologic study. *Scand J Gastroenterol* 1992;**27**:793–8.
12 **Roseth AG**, Schmidt PN, Fagerhol MK. Correlation between faecal excretion of indium-111-labelled granulocytes and calprotectin, a granulocyte marker protein, in patients with inflammatory bowel disease. *Scand J Gastroenterol* 1999;**34**:50–4.
13 **Ton H**, Brandsnes, Dale S, *et al*. Improved assay for fecal claprotectin. *Clin Chim Acta* 2000;**292**:41–54.
14 **Johne B**, Kronborg O, Ton HJ, *et al*. A new calprotectin test for colorectal neoplasia. Clinical results and comparison with previous method. *Scand J Gastroenterol* 2001;**36**:291–6.
15 **Assad F**. Measles: Summary of worldwide impact. *Rev Infect Dis* 1983;**5**:452–9.
16 **Gershon A**. Measles (Rubeola). In: Fauci AS, Braunwald E, Isselbacher KJ, *et al*, eds. *Harrison's principles of internal medicine*, 14 Edn. New York: McGraw-Hill, 1998:1123–5.
17 **Ghosh S**, Armitage E, Wilson D, *et al*. Detection of persistent measles virus infection in Crohn's disease: current status of experimental work. *Gut* 2001;**48**:748–52.
18 **Wakefield AJ**, Pittilo RM, Sim R, *et al*. Evidence of persistent measles virus infection in Crohn's disease. *J Med Virol* 1993;**39**:345–53.
19 **Wakefield AJ**, Ekbom A, Dhillon AP, *et al*. Crohn's disease: pathogenesis and persistent measles virus infection. *Gastroenterology* 1995;**108**:911–16.
20 **Montgomery SM**, Morris DL, Pounder RE, *et al*. Paramyxovirus infections in childhood and subsequent inflammatory bowel disease. *Gastroenterology* 1999;**116**:796–803.
21 **Summers BA**, Appel MJ. Aspects of canine distemper virus and measles virus encephalomyelitis. *Neuropathol Appl Neurobiol* 1994;**6**:525–34.
22 **Reichelt WH**, Stensrud J-EM, Reichelt KL. Peptide excretion in celiac disease. *J Pediatr Gastroenterol Nutr* 1998;**26**:305–9.
23 **Sun Z**, Cade JR. A peptide found in schizophrenia and autism causes behavioral changes in rats. *Autism* 1999;**3**:85–95.
24 **Friedman DI**, Amidon GL. Oral absorption of peptides: influence of pH and inhibitors on the intestinal hydrolysis of leu-enkephalin and analogues. *Pharmaceutical Res* 1991;**8**:93–7.
25 **D'Eufemia P**, Celli M, Finocchiaro R, *et al*. Abnormal intestinal permeability in children with autism. *Acta Paediatr* 1996;**85**:1076–9.
26 **Horvath K**, Papdimitriou JC, Rabsztyn A, *et al*. Gastrointestinal abnormalities in children with autistic disorder. *J Paediatr* 1999;**135**:559–63.
27 **Anthony A**, Bjarnason I, Sigthorsson G, *et al*. Faecal calprotectin levels correlate with acute inflammation in autistic enterocolitis. *Gut* 2000;**46**(suppl II):A3.
28 **Bunn SK**, Bisset WM, Main MJ, *et al*. Fecal calprotectin: validation as a noninvasive measure of bowel inflammation in childhood inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2001;**33**:14–22.
29 **Bunn SK**, Bisset WM, Main MJ, *et al*. Fecal calprotectin as a measure of disease activity in childhood inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2001;**32**:171–7.
30 **Rugtveit J**, Fagerhol MK. Age-dependent variations in fecal calprotectin concentrations in children. *J Pediatr Gastroenterol Nutr* 2002;**34**:323–4.
31 **Furlano RI**, Anthony A, Day R, *et al*. Colonic CD8 and gamma delta T-cell infiltration with epithelial damage in children with autism. *J Pediatr* 2001;**138**:366–72.