

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

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Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder. **Methods** 12 children (mean age 6 years [range 3-10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Findings Onset of behavioural symptoms was associated, by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in another. All 12 children had intestinal abnormalities, ranging from lymphoid nodular hyperplasia to aphthoid ulceration. Histology showed patchy chronic inflammation in the colon in 11 children and reactive ileal lymphoid hyperplasia in seven, but no granulomas. Behavioural disorders included autism (nine), disintegrative psychosis (one), and possible postviral or vaccinal encephalitis (two). There were no focal neurological abnormalities and MRI and EEG tests were normal. Abnormal laboratory results were significantly raised urinary methylmalonic acid compared with age-matched controls ($p=0.003$), low haemoglobin in four children, and a low serum IgA in four children.

Interpretation We identified associated gastrointestinal disease and developmental regression in a group of previously normal children, which was generally associated in time with possible environmental triggers.

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In eight children, the onset of behavioural problems had been linked, either by the parents or by the child's physician, with measles, mumps, and rubella vaccination. Five had had an early adverse reaction to immunization (rash, fever, delirium; and, in three cases, convulsions). In these eight children the average interval from exposure to first behavioural symptoms was 6.3 days (range 1-14). Parents were less clear about the timing of onset of abdominal symptoms because children were not toilet trained at the time or because behavioural features made children unable to communicate symptoms.

One child (child four) had received monovalent measles vaccine at 15 months, after which his development slowed (confirmed by professional assessors). No association was made with the

vaccine at this time. He received a dose of measles, mumps, and rubella vaccine at age 4.5 years, the day after which his mother described a striking deterioration in his behaviour that she did link with the immunisation. Child nine received measles, mumps, and rubella vaccine at 16 months. At 18 months he developed recurrent antibiotic-resistant otitis media and the first behavioural symptoms, including disinterest in his sibling and lack of play.

Endoscopic findings

The caecum was seen in all cases, and the ileum in all but two cases. Endoscopic findings are shown in table 1. Macroscopic colonic appearances were reported as normal in four children. The remaining eight had colonic and rectal mucosal abnormalities including granularity, loss of vascular pattern, patchy erythema, lymphoid nodular hyperplasia, and in two cases, aphthoid ulceration. Four cases showed the "red halo" sign around swollen caecal lymphoid follicles, an early endoscopic feature of Crohn's disease.³ The most striking and consistent feature was lymphoid nodular hyperplasia of the terminal ileum which was seen in nine children (figure 2), and identified by barium follow-through in one other child in whom the ileum was not reached at endoscopy. The normal endoscopic appearance of the terminal ileum (figure 2) was seen in the seven children whose images were available for comparison.

Figure 2: Endoscopic view of terminal ileum in child three and in a child with endoscopically and histologically normal ileum and colon. Greatly enlarged lymphoid nodule in right-hand field of view. A and B=child three; C=normal ileum. Remainder of mucosal surface of terminal ileum is a carpet of enlarged lymphoid nodules. We describe a pattern of colitis and ileal-lymphoid-nodular hyperplasia in children with developmental disorders. Intestinal and behavioural pathologies may have occurred together by chance, reflecting a selection bias in a self-referred group; however, the uniformity of the intestinal pathological changes and the fact that previous studies have found intestinal dysfunction in children with autistic-spectrum disorders, suggests that the connection is real and reflects a unique disease process.

Asperger first recorded the link between coeliac disease and behavioural psychoses.⁴ Walker-Smith and colleagues⁵ detected low concentrations of alpha-1 antitrypsin in children with typical autism, and D'Eufemia and colleagues⁶ identified abnormal intestinal permeability, a feature of small intestinal enteropathy, in 43% of a group of autistic children with no gastrointestinal symptoms, but not in matched controls. These studies, together with our own, including evidence of anaemia and IgA deficiency in some children, would support the hypothesis that the consequences of an inflamed or dysfunctional intestine may play a part in behavioural changes in some children.

The "opioid excess" theory of autism, put forward first by Panksepp and colleagues⁷ and later by Reichelt and colleagues⁸ and Shattock and colleagues⁹ proposes that autistic disorders result from the incomplete breakdown and excessive absorption of gut-derived peptides from foods, including barley, rye, oats, and caesin from milk and dairy produce. These peptides may exert central-opioid effects, directly or through the formation of ligands with peptidase enzymes required for breakdown of endogenous central-nervous-system opioids,⁹ leading to

disruption of normal neuroregulation and brain development by endogenous encephalins and endorphins.

One aspect of impaired intestinal function that could permit increased permeability to exogenous peptides is deficiency of the phenyl-sulphur-transferase systems, as described by Waring.¹⁰ The normally sulphated glycoprotein matrix of the gut wall acts to regulate cell and molecular trafficking.¹¹ Disruption of this matrix and increased intestinal permeability, both features of inflammatory bowel disease,¹⁷ may cause both intestinal and neuropsychiatric dysfunction. Impaired enterohepatic sulphation and consequent detoxification of compounds such as the phenolic amines (dopamine, tyramine, and serotonin)¹² may also contribute. Both the presence of intestinal inflammation and absence of detectable neurological abnormality in our children are consistent with an exogenous influence upon cerebral function. Lucarelli's observation that after removal of a provocative enteric antigen children achieved symptomatic behavioural improvement, suggests a reversible element in this condition.¹³

Despite consistent gastrointestinal findings, behavioural changes in these children were more heterogeneous. In some cases the onset and course of behavioural regression was precipitous, with children losing all communication skills over a few weeks to months. This regression is consistent with a disintegrative psychosis (Heller's disease), which typically occurs when normally developing children show striking behaviour changes and developmental regression, commonly in association with some loss of coordination and bowel or bladder function.¹⁴ Disintegrative psychosis is typically described as occurring in children after at least 2-3 years of apparently normal development.

Disintegrative psychosis is recognised as a sequel to measles encephalitis, although in most cases no cause is ever identified.¹⁴ Viral encephalitis can give rise to autistic disorders, particularly when it occurs early in life.¹⁵ Rubella virus is associated with autism and the combined measles, mumps, and rubella vaccine (rather than monovalent measles vaccine) has also been implicated. Fudenberg¹⁶ noted that for 15 of 20 autistic children, the first symptoms developed within a week of vaccination. Gupta¹⁷ commented on the striking association between measles, mumps, and rubella vaccination and the onset of behavioural symptoms in all the children that he had investigated for regressive autism. Measles virus^{18,19} and measles vaccination²⁰ have both been implicated as risk factors for Crohn's disease and persistent measles vaccine-strain virus infection has been found in children with autoimmune hepatitis.²¹

We did not prove an association between measles, mumps, and rubella vaccine and the syndrome described. Virological studies are underway that may help to resolve this issue.

If there is a causal link between measles, mumps, and rubella vaccine and this syndrome, a rising incidence might be anticipated after the introduction of this vaccine in the UK in 1988. Published evidence is inadequate to show whether there is a change in incidence²² or a link with measles, mumps, and rubella vaccine.²³ A genetic predisposition to autistic-spectrum disorders is suggested by over-representation in boys and a greater concordance rate in monozygotic than in dizygotic twins.¹⁵ In the context of susceptibility to infection, a genetic

association with autism, linked to a null allele of the complement (C) 4B gene located in the class III region of the major-histocompatibility complex, has been recorded by Warren and colleagues.²⁴ C4B-gene products are crucial for the activation of the complement pathway and protection against infection: individuals inheriting one or two C4B null alleles may not handle certain viruses appropriately, possibly including attenuated strains.

Urinary methylmalonic-acid concentrations were raised in most of the children, a finding indicative of a functional vitamin B12 deficiency. Although vitamin B12 concentrations were normal, serum B12 is not a good measure of functional B12 status.²⁵ Urinary methylmalonic-acid excretion is increased in disorders such as Crohn's disease, in which cobalamin excreted in bile is not reabsorbed. A similar problem may have occurred in the children in our study. Vitamin B12 is essential for myelinogenesis in the developing central nervous system, a process that is not complete until around the age of 10 years. B12 deficiency may, therefore, be a contributory factor in the developmental regression.²⁶

We have identified a chronic enterocolitis in children that may be related to neuropsychiatric dysfunction. In most cases, onset of symptoms was after measles, mumps, and rubella immunisation. Further investigations are needed to examine this syndrome and its possible relation to this vaccine.

Addendum:

Up to Jan 28, a further 40 patients have been assessed; 39 with the syndrome.

Contributors

A J Wakefield was the senior scientific investigator.

S H Murch and M A Thomson did the colonoscopies.

A Anthony, A P Dhillon, and S E Davies carried out the histopathology.

J Linnell did the B12 studies.

D M Casson and M Malik did the clinical assessment.

M Berelowitz did the psychiatric assessment.

P Harvey did the neurological assessment.

A Valentine did the radiological assessment.

JW-S was the senior clinical investigator.

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