1998 Wakefield MMR Controversy

The Australian Experience

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

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Summary

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 encephalitides (two). There were no focal neurological abnormalities and MRI and EEG tests were normal. Abnormal laboratory results were significantly raised urinary methionylalanine 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.

See Commentary page 611

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Introduction

We saw several children who, after a period of apparent normality, lost acquired skills, including communication. They all had gastrointestinal symptoms, including abdominal pain, diarrhoea, and bloating and, in some cases, food intolerance. We describe the clinical findings, and gastrointestinal features of these children.

Patients and methods

12 children, consecutively referred to the department of paediatric gastroenterology with a history of a pervasive developmental disorder with loss of acquired skills and intestinal symptoms (diarrhoea, abdominal pain, bloating and food intolerance), were investigated. All children were admitted to the ward for 1 week, accompanied by their parents.

Clinical investigations

We took histories, including details of immunisations and exposure to infectious diseases, and assessed the children. In 11 cases the history was obtained by the senior clinician (JW-S). Neurological and psychiatric assessments were done by consultant staff (PH, MB) with HMS-4 criteria. Developmental histories included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospitals; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SH or MAT under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsies were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRI), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

Laboratory investigations

Thyroid function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known causes of childhood neurodegenerative disease. Urinary methionylalanine was measured in random urine samples from eight of the 12 children and 14 age-matched and sex-matched normal controls, by a modification of a technique described previously. Chromatograms were scanned digitally on computer, to analyse the methionylalanine zones from cases and controls. Urinary methionylalanine concentrations in patients and controls were compared by a two-sample t test. Urinary creatinine was estimated by routine spectrophotometric assay.

Children were screened for antietiomyosal antibodies and boys were screened for fragile-X if this had not been done.
### AUSTRALIAN STANDARD VACCINATION SCHEDULE
(November 1996)

<table>
<thead>
<tr>
<th>Age</th>
<th>Disease</th>
<th>Vaccine</th>
<th>Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months</td>
<td>Diphtheria, tetanus, pertussis</td>
<td>DTPw*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poliomyelitis</td>
<td>OPV-Sabin vaccine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hib</td>
<td>Hib vaccine (HbOC or PRP-OMP)**</td>
<td></td>
</tr>
<tr>
<td>4 months</td>
<td>Diphtheria, tetanus, pertussis</td>
<td>DTPw*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poliomyelitis</td>
<td>OPV-Sabin vaccine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hib</td>
<td>Hib vaccine (HbOC or PRP-OMP)**</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>Diphtheria, tetanus, pertussis</td>
<td>DTPw*</td>
<td>first 6 months</td>
</tr>
<tr>
<td></td>
<td>Poliomyelitis</td>
<td>OPV-Sabin vaccine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hib (HbOC schedule only)</td>
<td>Hib vaccine (HbOC)</td>
<td>second 12 months</td>
</tr>
<tr>
<td>12 months</td>
<td>Measles, mumps, rubella</td>
<td>MMR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hib (PRP-OMP schedule only)</td>
<td>Hib vaccine (PRP-OMP)</td>
<td>third 18 months</td>
</tr>
<tr>
<td>18 months</td>
<td>Diphtheria, tetanus, pertussis</td>
<td>DTPa or DTPw</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poliomyelitis</td>
<td>Hib vaccine (HbOC)</td>
<td></td>
</tr>
<tr>
<td>Prior to</td>
<td>Diphtheria, tetanus, pertussis</td>
<td>DTPa or DTPw</td>
<td></td>
</tr>
<tr>
<td>school entry-4-5 years</td>
<td>Poliomyelitis</td>
<td>OPV-Sabin vaccine</td>
<td></td>
</tr>
<tr>
<td>10-16 years</td>
<td>Measles, mumps, rubella</td>
<td>MMR</td>
<td></td>
</tr>
<tr>
<td>1 month later</td>
<td>Hepatitis B (2nd dose)</td>
<td>HBV</td>
<td></td>
</tr>
<tr>
<td>6 months after 1st dose</td>
<td>Hepatitis B (3rd dose)</td>
<td>HBV</td>
<td></td>
</tr>
<tr>
<td>Prior to</td>
<td>Diphtheria, tetanus, pertussis</td>
<td>Td (ADT)**</td>
<td></td>
</tr>
<tr>
<td>leaving school-15-19 years</td>
<td>Poliomyelitis</td>
<td>OPV-Sabin vaccine</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- DTP is the abbreviation for Diphtheria-Tetanus-Pertussis vaccine.
- HibOC is ‘HibTITER’, PRP-OMP is ‘Pedvax® Hib’.
- Hib vaccine (HbOC) is given at 2, 4, 6, and 18 months.
- Hepatitis B (HbOC) is given at 1 month and 6-12 months.
- OPV-Sabin vaccine is given at 2, 4, and 6 months.

### INTERIM HEPATITIS B SCHEDULE FOR INFANTS

The NHMRC has endorsed the use of hepatitis B vaccine (HBV) for all infants. HBV should be administered at birth, 1 month, and 6-12 months of age. Hepatitis B vaccine has not yet been included in the standard infant schedule because it is only available as an additional injection. Parents who express an interest in infant HBV should be encouraged to have their children vaccinated, as long as compliance with schedule vaccines is not jeopardised.

The NHMRC strongly recommends that HBV be offered to all infants born to HbsAg+ mothers and to all infants and young children from groups with a hepatitis B carrier rate of over 2% (see Section 3.8).
Australian National Immunisation Programme in 1998

Australian Immunisation program for children under 5 years: provider type

- Public sector
- General practice
Australian National Immunisation Programme in 1998

Australian child vaccination rates

How?

- $ parents
- $ general practice
- National register (ACIR) to monitor targets
- Campaigns and research
- School entry record checks

1995: 53%

2008: 92%
What happened in the UK?

Feb 1998
Wakefield paper published describing new enterocolitis “syndrome” in autistic children, linked to Measles vaccine by parental recall

“...I have to say that there is sufficient anxiety in my own mind of the safety, the long term safety of the polyvalent, that is the MMR vaccination in combination, that I think that it should be suspended in favour of the single vaccines....” - Andrew Wakefield, New Release Video, 1998

1998 onwards
Wide UK media coverage

- The Guardian
- Evening Standard

Document Count UK
Factiva Search
What happened in the UK?

1998 – 2000’s
Becomes a political issue in UK

2000 onward
MMR coverage in UK drops to 80% in 2003-04, 1144 cases in UK 2009

2004 - 2010
Brian Deer Investigation

Revealed: MMR research scandal
ST investigation exposes scientist’s ‘fatal’ conflict of interest
What happened

2004
10 of original paper authors issues partial retraction of paper in Lancet

2007-2010
GMC found Wakefield found guilty of “dishonesty and irresponsibility” and banned from practice due to the “serious and wide-ranging findings against him”

2010
Lancet fully retracts 1998 article
Meanwhile in Australia……

- MMR coverage remained stable and disease low

Unlike in the UK….

Meanwhile in Australia......

• Nowhere near the same level of media coverage

![Graph showing document count for UK and Australia from 1998 to 2003.]

• Although some evidence that some providers accepted the MMR / autism link

Table 3: Beliefs about MMR vaccine among NSW regional health professionals.

<table>
<thead>
<tr>
<th>Beliefs about an association between MMR vaccine and each condition</th>
<th>Inflammatory bowel disease</th>
<th>Autism</th>
<th>Idiopathic thrombocytopenic purpura</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>17</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>unsure</td>
<td>37</td>
<td>29</td>
<td>45</td>
</tr>
<tr>
<td>no</td>
<td>59</td>
<td>59</td>
<td>48</td>
</tr>
</tbody>
</table>

Note:
(a) Weighted percentages

## MMR scare: UK versus Australia

<table>
<thead>
<tr>
<th>UK</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wakefield was a “home grown” champion of MMR / autism theory</td>
<td>No local “champion” of the theory</td>
</tr>
<tr>
<td>Media coverage “extensive and sustained”</td>
<td>Media coverage “sporadic”</td>
</tr>
<tr>
<td>“Grandstanding” by member of UK conservative opposition party, and then-prime minister refused to divulge whether his son was vaccinated</td>
<td>Consistent strong bipartisan political support for immunisation</td>
</tr>
<tr>
<td>Public trust in government assurances already eroded by mis-handling of CJD</td>
<td>No such erosion of public trust</td>
</tr>
</tbody>
</table>

Adapted from Leask, J., Booy, R. & McIntyre, P; *MMR, Wakefield and The Lancet: What can we learn?* MJA 193(1) 5-7.
What were the learnings?

- Vaccine scares are inevitable
  - Should be planned for
  - Involve multiple stakeholders

- Communication
  - should involve interactive engagement with professionals, the public and the media
  - Media should be cautioned against providing “false balance” to unfounded criticisms

- Better vaccine safety surveillance and timely, transparent reporting

- Transparent research integrity