SEVERING THE LINK BETWEEN MMR AND AUTISM

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INTRODUCTION

The prevalence of autism and associated pervasive developmental disorders in the UK may be as common as six per 1,000,[1] making them far commoner than many other disabling conditions of childhood such as cerebral palsy and serious sensory impairment. They are no longer considered rare disorders,[2] and the 'autism community' – as termed in the recent MRC document *Review of Autism Research, Epidemiology and Causes*[3] – is rightly demanding that there is an urgent need for research into the causes of the condition for those children for whom there is, as yet, no established aetiology.

DETECTION OF AUTISTIC SPECTRUM DISORDER

Autism is primarily a disorder of empathy which is expressed through abnormal development of speech and language, problems of social interaction and imaginary thought with repetitive ritualised behaviours. The clinical picture is modified by age and intellect[4, 5] such that the repetitive ritualised behaviour may not be so evident in very young children, or children with higher intellectual function may have seemingly normal receptive and expressive language development but difficulties in the pragmatics or use of language. Recent developments in our understanding of the presentation in very young children, or in those who are intellectually able, has no doubt increased the recognised prevalence. Similarly, there is a far greater likelihood that children with severe and profound intellectual handicap in the 'special school' population will be diagnosed so that they can benefit from the helpful range of educational and behavioural interventions that are now available.[6] Thus this may be the first piece of the puzzle, a rising prevalence due to changes in diagnostic fashion. In the absence of an objective scientifically validated test, we rely on a behavioural construct to make a diagnosis, albeit refined with modern techniques such as the Autism Diagnostic Interview.[7, 8] Clinicians are getting cleverer at recognising the condition in all its guises, and thus the diagnostic rate has increased, but many remain concerned that the numbers may be increasing through another mechanism.

BOWEL DISORDER IN AUTISTIC SPECTRUM DISORDERS

Against this background Wakefield *et al.*[9] reported on 12 children with regressive pervasive developmental disorder and bowel symptoms and described findings of an ileal-lymphoid-nodular hyperplasia and non-specific colitis. Although the authors clearly stated that the association between the onset of the behavioural symptoms and the child's receipt of the measles, mumps and rubella (MMR) vaccine was one suggested and identified by the parents, they then devoted most of their discussion to speculation, with some reference to the evidence for this putative link. The article has been criticised but the medical community needs to acknowledge that this research was published in a peer-reviewed journal and, not surprisingly, was seized upon by the media. Reminiscent of the debate in the 70s over pertussis vaccine,[10] the road back to credibility for the MMR vaccine is proving a tough one.

Earlier this year these same researchers reported again on a potential viral pathogenic mechanism, for what they now termed 'new variant' inflammatory bowel disease in children with developmental disorder. Employing the reverse transcriptase polymerase chain reaction, they described measles virus within the follicular dendritic cells and some lymphocytes in foci, of reactive follicular hyperplasia in intestinal tissue. The commentary to this paper counsels that it would be 'entirely wrong to jump to the conclusion that the measles component of MMR "causes" the colitis or the developmental disorder'. They remind the readership that there are many instances where neurological disease results in a functional bowel disorder, and that disruption of neurotransmitters and mediators of inflammation may result in a failure to clear virus infections efficiently.[12]

As a cautionary tale one should recall that when measles and the MMR were linked with Crohn's disease, attempts were made to replicate original findings and there was a lack of confirmatory evidence. As the polymerase chain reaction in this research into Crohn's disease and autism and bowel disorder is exquisitely sensitive, false positives can still occur even with rigorous laboratory procedures.[13]

PUTATIVE MECHANISMS OF THE 'LEAKY' GUT

Nevertheless, supposing the presence of the measles virus in intestinal tissue in children with autism were to be replicated, there would still need to be a mechanism by which this could translate into the symptoms of autism. The one proposed by Reichelt[14–16] and Shattock[17] and referred to in the paper by Wakefield *et al.*[9] is that of the 'leaky gut' whereby the children develop an enteropathy triggered by some factor such as the MMR vaccine or measles and then mediated by gluten sensitivity. This is said to lead to abnormal absorption of exogenous opioid peptides derived from food products such as casein, which enter the child's circulation, cross the blood brain barrier and exert an effect on the opioid receptors of the brain

giving rise to the autistic symptoms. These research groups have described similar findings of urinary peptiduria on High Pressure Liquid Chromatography in untreated coeliac patients and in children with autism who are following exclusion diets omitting gluten and dairy products.[18,19] This research is given a wide exposure to the 'autism community'.* Accardo has described the adoption of these exclusion diets in autism as having reached epidemic proportions.[20]

However, what needs to be reconciled with these findings is that the incidence of gluten sensitivity and coeliac disease is no greater in the autistic population[21] than in the general population. In addition, the exogenous opioid peptiduria has not been replicated by other groups.[22] Within the complex environment of the low molecular compounds of urine neither high pressure liquid chromatography or mass spectrometry alone would appear to allow accurate identification of these peptides in urine.[23]

Therefore, whilst there is certainly some evidence that opioid peptides in animal models cross the blood brain barrier, activate opioid receptors in the brain and give rise to symptoms considered similar to those involved in autism, these may be endogenously derived.[24] Certainly, the evidence that these are exogenously derived and triggered by the MMR in autism is lacking.

EPIDEMIOLOGICAL STUDIES

In contrast there are many epidemiological studies which do give a good body of evidence and this is all against a link between MMR and autism.[25–8] These have been authoritatively reviewed by a number of authors and scientific bodies.[3,29,30] One such large regional sample of children with autism showed no increase in the condition following the introduction of MMR, no difference in the age of diagnosis between those children who had received MMR and those who had not, no difference in the immunisation rate between children affected by autism and the general population and no link between the timing of the MMR vaccine and the onset of the child's autism.[31] Other large studies have shown no association between inflammatory bowel disease and autism amongst those children immunised with MMR, whilst a large UK general practice research database found no relationship between the rise in the incidence of autism and the introduction of the MMR vaccine.[32] In addition, children who become autistic do not consult more often with their GP after receipt of the MMR vaccine than those who do not become autistic.[33]

MMR AND HERD IMMUNITY

The evidence is overwhelmingly in favour of administering the MMR vaccine as presently advocated, with the first dose at 12–15 months followed by the second dose between three to five years as part of the pre-school booster programme.[30] This recommendation has the weight of many organisations[34] who endorse the excellent safety record of the vaccine, which has been administered to many millions of children for over 25 years. These organisations have appraised the evidence and produced a range of publications aimed at securing public confidence.[29]

Herd immunity, i.e. the immunity of a community, depends on a critical mass of immunised persons: in the case of measles, 90–5% of the population have to be immunised. This is highly susceptible to negative coverage in the popular press. When immunisation levels fall below this level, the most vulnerable children such as the infant under one year (before the first dose) and the immunocompromised child cannot be protected from measles, a disease that results in one in 1,000 children suffering with meningitis/encephalitis and in one to two deaths per 1,000. Neither can protection be offered to the two per cent of pregnant women who are not immune to rubella and whose baby runs a 90% risk of birth defects, if infected in the early part of pregnancy. Additionally, there is no protection against mumps – the commonest cause of viral meningoencephalitis in the under 15 year olds – which can result in permanent hearing loss and inflammation of the testes in four out of ten adult males.[35]

SEVERING THE LINK

Herd immunity is already falling and subsequently resulting in well-described outbreaks of disease.[36] Under the bombardment of the media[37] and medical press some professionals are wavering – so it is not surprising that parents do similarly.[38] It will possibly need to run its course as was the case with pertussis. Some are advocating a pragmatic view of making single vaccines available,[37] a move that would no doubt be seen as capitulation by many members of the public and the media, and further decrease confidence in the safety of the MMR vaccine. The single vaccine is fraught with difficulties such as compliance in the face of six inoculations and uncertainty with respect to efficacy, availability and degree of immunity, but it is not even a logical move when one considers that the published research concentrates on the measles virus.

One certainly sympathises with parents over all these issues, and it is unrealistically time consuming to go over it all with every parent agonising over whether to take up the MMR.[39,40] The NHS Scotland MMR information pack is clearly laid out and may help.[35,41] A strong conviction of the benefits and safety of MMR laid out by the family GP may sway parents, but at the end of the consultation they may recall the newspaper advert instead,[42] decline the MMR vaccine and make the wrong decision.[43] The irony is that they make it from the best of motives.[44]

* The paper entitled 'Evaluation of Urinary Profiles obtained from people with Autism and associated Disorders. Part 2: The role of Vaccines in the causation of Autism and related disorders' can be viewed online at: http://osiris.sunderland.ac.uk/autism/vaccine.htm#Shattock.

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